MORGAGNI'S SYNDROME

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Hyperostosis frontalis interna, Virilismus, Obesitas

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Frontispiece



GIOVANNI BATTISTA MORGAGNI

1682–1771

PREFACE

THIS monograph is a comprehensive account of the author's investigations of Morgagni's syndrome and contains in addition much clinical and anatomical material not as yet published. My interest in frontal hyperostosis dates from 1930, and my first observations were published in a lecture in the summer of 1935, followed by several smaller works and lectures in English, French, German, and Swedish during the years 1935-1945. A monograph written in German in 1937 and a paper in 1944 contain more detailed accounts of the subject.

Fourteen years ago, when I started these investigations, the literature on frontal hyperostosis was limited and easy to survey ; today it includes about 250 larger works and smaller papers, some of them difficult to get It would, therefore, seem desirable to bring together all these various studies in as complete a form as possible for correlation and review of the results obtained.

In 1936, as an act of homage to the great Morgagni, " the father of the anatomo-pathological manner of thinking," who was the first to describe this syndrome, I proposed the name Morgagni's Syndrome ; this suggestion has been almost generally adopted

In this place I wish to express my sincere gratitude to Dr Sherwood Moore, Professor of Radiology, Washington University School of Medicine, and Director of the Edward Mallinckrodt Institute of Radiology, St Louis, Missouri, U S A., who has given me the incentive to publish this English monograph I feel it is a great honour that so prominent a roentgenologist as Dr Moore has consented to write an introduction to this edition.

To my friend, Professor Matthew J. Stewart of Leeds, my warmest thanks are due for all the good advice he has given me.

I am deeply indebted to Professor A Murray Drennan of Edinburgh and to his son Dr James M. Drennan for all the help they have so unstintingly given me in correcting the English of my manuscript, and to Professor J C. Brash for his help in checking the translations of Latin texts

FOLKE HENSCHEN

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INTRODUCTION

Ever since Professor Folke Henschen kindly sent me his monograph, "Morgagni's Syndrome: *Hyperostosis frontalis interna, Virilismus, Obesitas,*" I have hoped that this work might be made more widely available to the medical profession of the English-speaking world. Happily, this hope is now fulfilled.

It is indeed gratifying that Professor Henschen graciously requested that I write an introduction. Anyone who is familiar with his fine attainment will realize that it requires no introduction from me.

Morgagni's syndrome has a far higher incidence than is commonly supposed; it is often accompanied by great suffering and disability, ranging from minor semi-invalidism to almost total physical incapacity and even psychosis. Professor Henschen has thrown much light on the obscure etiology of this condition, and I am indeed happy to pay my tribute to his work which I regard as an outstanding contribution to science and to his colleagues in the medical profession.

SHERWOOD MOORE, M.D.

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ABBREVIATIONS

In this work the following abbreviations are used:

Syndromes

CS = Cushing's syndrome.
FS = Fröhlich's syndrome, Dystrophia adiposo-genitalis.
MS = Morgagni's syndrome (Henschen).
PMS = Pierre Marie's syndrome, Acromegaly.
PS = Pregnancy syndrome (Henschen).

Hyperostoses of the Skull

Hcd = Hyperostosis calvariæ diffusa (Moore)
Hfi = Hyperostosis frontalis interna.
Hfp = Hyperostosis fronto-parietalis (Moore).

Cells of the Anterior Pituitary Lobe

Ac = Alpha or acidophil cells
Bc = Beta or basophil cells
Cc = Chromophobe cells.

MORGAGNI'S SYNDROME

CHAPTER ONE

INTRODUCTION

THE term *Morgagni's Syndrome* indicates a triad of endocrine symptoms, namely Hyperostosis frontalis interna, Virilism and Obesity, occurring chiefly in older women. In 1936 we presumed to name this triad of frequently occurring changes, by themselves already well known, after MORGAGNI, because this great scientist was the first to describe clearly and objectively a classical example of the triad.

The hyperostosis frontalis, which may be regarded as the principal symptom, was briefly mentioned by MORGAGNI (Patavii, 1719) in his "Adversaria anatomica" [1]:

". . . ex eo potissimum conjeci quod in grandævæ muheris cranio etsi os frontis, & processus uterque petrosus, albidioris, atque adeo novæ osseæ substantiæ accessione, & quasi effusione multum, atque inæqualiter introrsum protuberabant, ac cerebrum comprimebant; quoniam tamen ea compressio paulatim facta, & aucta fuerat, nullo quidem illa cerebri vitio de quo nunquam conquesta erat, sed mucronis cordis ruptura . . . repente obiit."

English Translation.—"I have obtained evidence of this chiefly in the skull of a very old woman; although the frontal bone and both petrous processes (by the accretion of new, rather whiter bony substance, just as if it were an effusion) projected unequally inwards so that they compressed the brain, nevertheless the compression began and increased so gradually that there was no defect of the brain giving rise to any complaint, but from rupture of the apex of the heart—she died suddenly."

We find a complete description of the whole syndrome in the 27th anatomico-medical epistle of MORGAGNI'S "De Sedibus et Causis Morborum" (1761), in which the above-mentioned case is described in detail The relevant part reads in MORGAGNI as follows [2] :—

"Mulier annos nata quinque, & septuaginta, virili aspectu, & valde obesa, cum ad quinctum usque & quadragesimum annum fuisset gracilis; annis novissimis facta erat valetudinaria sic tamen, ut de capitis dolore nunquam, nedum de graviore ullo, quod referri ad ipsum posset, incommodo, quereretur." Death occurred rather unexpectedly in the midst of domestic duties. At the autopsy, carried out by MORGAGNI and SANTORINI, an intense arteriosclerosis and a rupture of the heart with tamponade were among the changes observed Of the skull lesions he writes: "Cranium denique reserantes, Crassam meningem animadvertimus tanto arctius quam soleat,

[1] "Adversaria anatomica sexta." Animadversio 84.
[2] Liber II, Epist Anat. Medica 27, Art. 2.

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departure, since the two other principal components of the triad, obesity and virilism, are much too frequent, ambiguous and non-characteristic. A syndrome is a concurrence of symptoms, "a set of symptoms which occur together" (Dorland's "American Medical Dictionary," 1939), and it would certainly seem justifiable to build up with these three components a definite triad or syndrome. The following pages will show whether or not this is so.

The Hfi, the leading or main lesion, has an extremely characteristic appearance which in pronounced cases can be demonstrated radiologically. Besides this, Hfi has the great advantage of being permanent and stable, which cannot be said of the other two components of the triad, the male hairiness and the obesity. There are not a few secondarily emaciated cases of MS in which the obesity is absent, while the male hairiness can very easily be removed. The coarse face and big hands and feet, which are rather more acromegaloid manifestations, may in their lesser degrees be difficult to judge or may even be completely lacking.

Thus with good reason the radiologically diagnosed Hfi forms the starting point in the many clinical reports on the presumptive symptomatology of MS, which have been published in recent years. Moniz in 1938 speaks of "the syndrome created in connection with the Hfi." Bartelheimer writes in 1939: "The Hfi provides an easily discoverable clinical sign, by which we may obtain a new point of view as to the origin of such endocrine symptoms as diabetes, polycythæmia and obesity." Knies and Le Fever have the same opinion (1941): "The cranial changes yet remain the central criteria of the disturbances, and are likely to remain its most pathognomonic sign, at least if the entire entity does not become submerged into a larger endocrinopathic field with broader and more definite characteristics" Even Louw (1943) thinks it "to be necessary to take the Hfi as the starting point, because no other trait in the large complex of symptoms is so constant." Only Mellgren (1942) seems not quite to agree with this "leading rôle" of the Hfi, in writing thus: "It does not seem to be quite consistent to consider the enostosis as the principal manifestation, as Henschen does, in which case a Cushingoid habitus could be conceived as a defective MS in which the enostoses are missing."

Everything is here dependent on definitions. In MS the Hfi is the integral component, which cannot and may not be missing. If the virilism or the obesity or eventually both are missing, one may have the right to speak of a defective MS, but an endocrine syndrome with virilism and obesity without Morgagni's hyperostosis cannot be noted as a defective MS. CS is not defective MS, but it is possible that MS represents a CS or a "piccolo Cushing" with Hfi. In this connection it may be expressly emphasized that the "leading rôle"

ad suturas, & prope suturas, præsertim Sagittalem, & Lambdoidem, affixam esse, ut sine laceratione avelli non potuerit, . . . Cum omnia e cranio exempta essent, cuius non mediocrem crassitudinem, sectionum latitudo ostendebat; in ejus basi, & in cava item facie ossis frontis ea in conspectum venerunt, de quibus in VI. Adversariis indicatum est. Scilicet os frontis ibi prominebat in confertissima tubera, qualia pariter in cranii basi, præsertim e Petrosis processibus, sed minora, atque disjecta se attollebant. Omnia ex substantia erant magis alba, quam usquam in toto cranio, ut ex nova osseæ substantiæ accessione, & quasi effusione facta esse viderentur. Quorum singulorum superficies etsi nitida erat, & lævigata; non potuerat tamen tanta universorum inæqualitas, & extuberantia non cerebrum valde comprimere, in quo cæteroquin nulla apparebat læsio, quacunque iis tuberibus responderat."

English Translation [1].—" A woman of 75 years of age, of a manly aspect, and very fat, having been quite slender to her forty-fifth year, was, in the latter years of her life, become a valetudinarian; yet in such a manner, as never to complain of a pain in her head, much less of any violent *indisposition that could be referr'd thereto. . At length having open'd* the cranium, we found the dura mater to be so much more closely affix'd to the sutures, and the parts about them, and particularly the sagittal and lambdoid, than it generally is, that it could not be pull'd away without laceration. . When all these contents were taken out of the cranium (which, as appear'd from the breadth of the sections, was not of a little thickness) on the basis of it, and also upon the hollow surface of the os frontis, those appearances came into view, which I have spoken of in the sixth of the 'Adversaria' (Animad 84). That is to say, the os frontis was prominent in that part, in the form of very frequent tuberosities: and the same kind of appearances were also in the basis of the cranium, especially on the petrose processes, but were less in these parts, at a greater distance from each other, and did not rise so high All these tuberosities were made up of a more white substance than the bones in any other part of the cranium were; so that they seem'd to consist of a new accession, and, as it were, an effusion of bony matter And though the surface of each of these prominences was very smooth, and shining, yet the very great inequality and extuberating state of them all, could not but extremely compress the brain, wherein there appear'd to be, in other respects, no kind of injury, in what part soever it corresponded with these tuberosities."

This case, described by MORGAGNI in a masterly manner, that of a woman, 75 years of age, of masculine appearance, very obese and with distinct hyperostosis frontalis, who, without having shown any clinical manifestations attributable to the intense cranial changes, dies of intercurrent disease—in this case rupture of the heart—is still to-day the prototype of the endocrine syndrome under discussion.

In the study of this syndrome it would seem advisable to choose hyperostosis frontalis, here regarded as the principal lesion, as the point of

[1] Translation from the Latin by Benjamin Alexander, M D, Vol 1, pp 832 and 834 London, 1769.

Here the general morphology of the Hfi will not be entered into, and for the present will be regarded as known. Diagnostic difficulties hardly exist in fully developed Hfi, in spite of the various appearances presented; the only conceivable one might be very strongly emerging ridges and marked depressions on the inner surface of the frontal bone corresponding with the convolutions of the brain, which, as is well known, occur rarely. The Hfi should not be confused with the pregnancy osteophyte, and in doubtful cases a microscopical examination should be done.

In earlier studies we have used for the designation of the different stages of the Hfi the following signs: for the early but indubitable Hfi, (+); for moderately developed Hfi, +; for Hfi of high degree, ++; and for Hfi of very high degree, +++. According to this, Hfi(+) signifies a slight, thin, level and often finely striated or slightly nodular osseous excrescence, mostly in front, below and medial, in the angle between the crest and orbital part of the frontal bone. In Hfi+ the changes are mostly dispersed over the inner side of the frontal bone, which is now distinctly knobby but still rather thin. By the term Hfi++ we understand an essentially thicker, more nodular and widely dispersed Hfi, which not infrequently goes beyond the coronal suture. Hfi+++ *signifies* a further development of the changes which may now be either strongly knobby, like a relief map, or smoother and more furrowed (Fig. 1). In these most pronounced cases hyperostotic changes are more frequent in the parietal bones than elsewhere. For more dubious cases, in which the collected series are not taken into consideration, the signification ? is used. These cases, however, have become more and more scanty with increasing experience

It may be emphasized in this connection that even the slight cases of Hfi are "definite" JACOBSEN and NIELSEN, who had at their disposal 12 cases, among them 2 autopsy cases, seem to doubt this in writing: "Cases showing very small changes predominate in HENSCHEN's material and thus the frequency is increased to 40 per cent., but if only those cases showing "definite" changes are considered, a frequency is obtained which approaches that of MOORE, that is to say, about 1·5 per cent." These authors do not seem to pay *attention to the fact that the radiological method of examination* in this condition must give lower figures than the pathological method which I employed Even the frequency of about 1·5 per cent., which they quote, is not in accordance with my experience. Taking only the cases signified by Hfi++ and Hfi+++ into account, my material gives a frequency of more than 11 per cent.

The complex of problems which MS and Hfi present includes a large group of fundamental problems and other more subsidiary ones, all of which will be discussed.

of the Hfi has an exclusively formal significance for purposes of classification only, and that, biologically speaking, certainly merits no greater importance than the other hormonal disturbances. These pituitary-conditioned polyglandular syndromes are so closely knit together that certain characteristic features must be selected to facilitate classification, such as the Hfi for MS.

The bone formation at the tabula interna of the frontal bone in MS is not quite specific, similar changes of the inner table of the skull also occurring in other syndromes, chiefly in acromegaly and pregnancy. This, however, does not diminish in any degree the clinical significance of Morgagni's hyperostosis but, on the contrary, seems to illuminate its obscure pathogenesis. These questions will be discussed more explicitly below.

The cases considered come for the most part from a big municipal hospital in Stockholm, the St Erik's Hospital, a minority from the clinics of the Seraphim Hospital and a further small number from the Caroline Hospital. Therefore one is entitled to say that the material is very representative of the population of Stockholm during the second world war. There are few foreign elements in the series, apart from individuals of more east-Baltic type. Some cases are of more or less Walloonic type, while the number of Jews comes to five at the most.

It is a great advantage to have material coming from several clinics, and at the St Erik's Hospital there are, besides medical clinics, a large surgical and a large psychiatric one.

It is expressly emphasized that this monograph is written by a pathologist who has at his disposal a large bulk of autopsy material, having regard to Swedish conditions. My experience has been gained, therefore, for the most part from the autopsy table and the pathological laboratory. The clinical reports, which were kindly put at my disposal by my colleagues, only exceptionally took into account a possible Hfi. This gives point to the diagnostic difficulties to be discussed more closely below, and serves to show that the post-mortem examination renders possible the discovery, observation and exact determination of commencing, slight or abortive Hfi, which in the author's opinion is hardly to be appreciated in the X-ray picture. The inclusion of the frequently occurring quite slight cases into the author's material has undoubtedly raised the frequency of the Hfi enormously, but, on the other hand, the most pronounced cases are by no means more frequent than in the collections of material from other countries.

The present work deals chiefly with Morgagni's hyperostosis. Other forms of hyperostoses of the skull, in particular Moore's Hed and Hfp, and the puerperal osteophyte, are taken into consideration only when they are of interest and importance in the understanding of the Hfi

CHAPTER TWO

SURVEY OF THE LITERATURE

BETWEEN the first full descriptions of hyperostosis frontalis published by MORGAGNI in 1719 and 1761 (see p. 1) and the publication of further data on this striking change in the skull there seems to have been a very long interval.

The earlier literature contains a short notice by GEORGET (1820), who seems to have observed Hfi in elderly women. A thickening of the skull was found in one-twentieth of 500 skulls of insane subjects. "I frequently observed that only the frontal bone presented this massive nutritive accretion, whereas the other bones were normal. . . These changes are commonest in old and sick female subjects."

BROUSSAIS (1828) emphasized the high percentage of incidence of Hfi

BRUNS' Atlas (1853) contains an illustration of the bone change.

WALLMANN (1858) described different forms of endocranial osteophytes, though without discussing in detail the Hfi

In his work "Die krankhaften Geschwulste" (1865), VIRCHOW discussed at length "Exostoses of the Skull" and even gave a concise and clear description of the Hfi "Even the intracranial exostoses of the skull show a similar versatility The smaller ones usually are more compact irrespective of whether they are flat or nodular (see preparation 411 of our collection), two types which are most commonly found in the frontal bone. The larger ones often are interiorly of spongy character, whereas their surface is compact. The largest ones are mostly ebony-like and their surface is hummocky, nodular or peculiarly twisted."

In 1869 BIRKETT gave a good description of the Hfi He assumed that this condition was due to new formation of bone in the diploe and destruction of the inner table He reported on four crania of female subjects, one of whom was insane

In a paper on senile changes of the skull (1870) SAUVAGE described the Hfi briefly To this paper we shall return later

ENGEL (1870) dealt extensively with "The Osteophyte on the Inner Surface of the Skull" The "uneven, warty, nodular and furrowed osteophytes" which are usually only encountered on the frontal portion of the frontal bone and the inferior portions of the bones of the lateral wall, and which "almost exclusively occur in individuals of an advanced age," are mentioned as a peculiar form of this condition. According to ENGEL neither the anatomical nor the clinical examination furnished any evidence in support of the assumption that they were related to any disease. In most of the cases they were accidentally found at autopsy, and "if symptoms of very vague character were manifested—which frequently is the case—the

1. The first question, which must have as clear an answer as possible because of its fundamental importance, is: What is the morphological and pathogenetic relation between Hfi and the many other skull changes which can be combined with or mistaken for it, principally Moore's Hcd and Hfp, but also the enostosis in acromegaly and the osteophyte in pregnancy? Does the hyperostosis of Morgagni hold an exclusive pathogenetic and pathognomonic position, enabling one to build up a syndrome on it, or is it only a morphological variation of other cranial changes without particular biological interest?

2. A second fundamental question, closely connected with the first, concerns the correlation between the Hfi and the other two components of the triad of Morgagni, virilism and obesity: Is this correlation distinct enough to justify biologically a special endocrine syndrome, MS?

3. Thirdly: What do we know about the frequency of the Hfi, its occurrence in the different stages of life and its distribution between the sexes?

4. In connection with the last question is the matter of the diagnostic value, in slight or commencing Hfi, of the clinical X-ray and the autopsy examination

5. Perhaps the most important question of all concerns the eventual clinical picture of MS and Hfi: Are MS and Hfi accompanied by a characteristic clinical symptomatology as most clinicians believe? Are the skull changes and the clinical manifestations closely connected to each other in a common complex of neuropituitary disturbances, or may not the very often co-existing senility, hypertension, arteriosclerosis and obesity, with their consequences in patients with Hfi, rather be the cause of the extraordinarily variable but—according to many authors—nevertheless characteristic symptomatology? Has the Hfi in itself any clinical significance at all?

6. Still awaiting solution is the question of the actual pathogenesis of Hfi together with such related matters as the functional connection of the pituitary gland and the adjacent cerebral parts, and also the presence or absence of any characteristic changes in the other endocrine organs, especially the sex glands and the suprarenal cortex.

7. Finally, we shall discuss the relation of MS to other generally acknowledged pituitary syndromes, namely, PMS, CS, FS and to the PS, a term suggested by us

A host of subsidiary considerations arising out of the main problems at issue will be discussed in the course of the paper.

ROBERTSON'S "Textbook of Pathology" (1900) contains data on the great frequency of thickening of the skull in insane subjects. Out of 304 cases examined not less than 50 per cent. were said to have presented changes of this type, though it cannot be appreciated from the data how many of these were cases of Hfi

RIBBERT'S textbook (1902) brings forward evidence that this author was familiar with the Hfi "It is of not uncommon occurrence that jagged outgrowths, occasionally even hemispherically rounded projections, develop on the inner surface of the skull, particularly of the frontal bone (during pregnancy and without any known reason)" It should be mentioned, however, that RIBBERT'S Fig. 440 is not very characteristic.

SHATTOCK (1913) published a comparatively large number of cases under the heading "Thickening of the Calvaria in the Insane," a designation which was characteristic of the generally prevailing view Among the 11 cases coming from different quarters there were 10 females; in 1 case sex and age were not stated. The great majority of the cases were individuals above 55 years One instance was that of a female aged 48 years who for eight years had been the subject of dementia Another case was that of a woman aged 37 years who was obese, insane and suffered from epilepsy. Pathogenetically, SHATTOCK'S view is consistent with that advanced by CLOUSTON and BEADLES. He considered alcoholism, which was present in some of his cases, as a contributive factor On the other hand, he seemed to attribute only a minor significance to the rather common coexistence of atrophy of the brain.

In SCHLESINGER'S paper (1914) on diseases occurring in individuals in advanced years, Hfi is briefly referred to. According to this author the internal table frequently is uneven, particularly in the area of the frontal bone, and occasionally presents marked, rough, hard, streaky or warty prominences.

NAITO and SCHULLER (1923) and NAITO (monograph, 1924) were *the first to examine the Hfi radiologically* Hyperostosis of the frontal bone is labelled as "compensatory" hyperostosis The "most commonly occurring types of these" are, according to these authors, "(1) hyperostotic microcephalus, (2) hyperostosis associated with cerebral infantile paralysis, idiocy, epilepsy [illegible]

the form of headaches, occasionally even of epilepsy The cases reported comprise 10 cases of "enostosis of the frontal bone" which were radiologically examined Some of these came from lunatic asylums Nine were cases of [illegible] an [illegible] of the brain was present, especially of the frontal lobes Warty excrescences were present even in the anterior and middle cranial grooves Case 2. A female aged 76 years whose skull was generally thickened and presented massive, bulging Hfi There was calcification of the falx cerebri Case 3 A female aged 53 presenting pronounced Hfi. Case 4 A female aged 62 presenting diffuse thickening of the skull and Hfi Case 5. An insane female presenting massive Hfi measuring 2 cm in thickness. Case 6 An insane

clinical diagnosis was in the majority of the cases a prophecy post festum; in other words, *if at the examination of a cadaver osteophytes are found, one is inclined to believe that one has found the explanation of certain symptoms referable to nervous and mental diseases.*[1] It is true that osseous formations frequently occurred in the presence of a morbid brain, but the pathological symptoms manifested during life were due to the brain disease and not to the new formation of bone. . . . The osteophyte has . . . until the beginning of old age a wholly physiological significance; it is not a causative agent but a consequence of the changes in the volume and form of the brain" It cannot, therefore, give rise to any such phenomena as pain and other symptoms.

FOLLIN and DUPLAY (1874) discussed the presumable symptomatology of the Hfi In some instances manifestations were absent In others, however, severe cerebral symptoms were manifested, viz, headaches, epileptiform convulsions, amaurosis, deafness as well as symptoms referable to meningitis and cerebral hæmorrhage.

LEGOUEST and SERVIER (1879) described 4 cases of Hfi. One of these was the case of a woman, in the other the sex was not noted.

POZZI (1879) described 4 cases of Hfi One of these was a female subject, in the remaining 3 cases data on sex were missing

TERRIER and LUC (1881) were the first to support the view that the Hfi

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mortems of the brain accumulated in an asylum. From the results of this investigation he infers that "bony outgrowths from the inner aspect of the calvaria are infrequent enough, or only about 1 per cent."

To HUMPHRY (1890) we owe the description of 2 cases of Hfi. One of these was the case of a woman aged 73 who died of apoplexy, and the other was that of a woman aged 90 In both cases a moderate atrophy of the parietal bones coexisted

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case because it might have given rise to compensatory new formation of bone.

BEADLES (1898) investigated "the cranium of the insane" in 144 male and 90 female cases. He found the presence of a more or less pronounced thickening of the skull in 22 males and 19 females The thickening was much more pronounced in females than in males, especially in the frontal region.

cases one of acromegaly associated with obesity in a woman aged 40; data on hair-growth are lacking MOREL (1930) looks upon this as a case of Hfi. The post-mortem revealed small thick exostoses on the inner surface of the frontal bone and the presence of a large cystic tumour of the hypophysis

[1] Italicized by F. H.

whose age was estimated at 50 years at least, or perhaps even between 60 and 70, presented a typical and fairly marked Hfi (Fig. 99) SCHREINER reported in brief that he had encountered a similar alteration before in a woman aged 72. On the occasion of the demonstration in 1907 of the hyperostotic skull, HARBITZ reported 3 similar cases in women which were detected at the autopsy; two of these were nulliparæ. We shall return to

were the subjects of ulcerous endocarditis These younger women form a distinct group Subsequently there was an interval of eleven years in DRESSLER's material of hyperostoses without post-mortem cases. Out of the older women 10 were aged between 50 and 59, 20 between 60 and 69, 17 between 70 and 79 and 1 between 80 and 90 Seven men were aged between 47 and 70 years.

addition to this factor which, in certain cases, may cause hyperostosis frontalis DRESSLER assumed that the backward displacement of the entire cerebrum during prolonged decubitus dorsalis was one of these · "Even if no considerable diminution of the volume of the brain occurs, the backward displacement of the frontal brain will elicit a sufficiently strong relaxing action on the part of the superposed bone" DRESSLER's microscopic examinations will be discussed later

To GREIG (1928) all credit is due for his comprehensive and important study of 188 museum specimens, out of which 32 (or 17 per cent) showed Hfi. The alteration was commonest in women in advanced years (the ratio of males to females was 1 7) He states that the skulls of females

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acromegaly coexisted. She had suffered from acromegaly from the age of 14 years The menopause occurred at 45 The pars frontalis showed nodular

male subject aged 50 years presenting a heavy and thick skull and pronounced Hfi. Case 7. A female aged 75 years presenting a thick skull and massive nodular Hfi. Case 8. A female aged 70 years presenting pronounced and typical Hfi. Case 9. A female aged 82 years presenting a tumour of the hypophysis (acromegaly) and extreme Hfi which was nodular on the internal aspect The pituitary tumour was verified at the operation. According to NAITO the most interesting feature of this case was "the coexistence of a tumour of the hypophysis with hyperostosis frontalis, a condition which must be assumed to have been predominantly or even exclusively senile" Roentgenograms of the skull furnished "hardly any evidence" of acromegalic alterations. Case 10 A female aged 59 years presenting diffuse hyperostosis of the roof of the skull as well as Hfi. The clinical picture suggested the presence of a tumour of the hypophysis The sella was radiologically normal

Out of NAITO's 9 cases of acromegaly the last one is that of a woman aged 57, presenting a typical Hfi but otherwise only a moderate thickening of the roof of the skull. In Case 4, a man aged 43 years, the frontal bone was thickened but there was no X-ray evidence of Hfi.

The case reported by MARCHAND and BAUER (1925) may have been a case of Hfi.

[illegible]

of the senile sclerosis and hyperostosis of the skull. "The most common of these alterations appears as concentric thickening of the anterior half of the skull It has either the aspect of a uniform accretion of the thickness of the wall, a process in which the diploe as well as the lamina partake, or there are bulging and plateau-shaped projections on the inner surface of the frontal bone which, in the majority of the cases, are wholly symmetrically orientated beside the furrow of the sinus longitudinalis" The paper contains plates illustrating the anatomical and radiological picture of the Hfi In four instances sex and age were noted They were cases of females aged 60, 62, 70 and 75 years respectively.

KNAGGS (1926) seemed to assume that the bone changes were, in certain cases at least, due to inflammatory processes or periostitis

LERI and COTTENET (1926) described changes "as being cases of specific and more or less marked osteitis of the internal table of the skull" which were characteristic of Hfi, at least partly These authors published a plate of the roof of a skull illustrating a typical and extreme case of Hfi which, however, was assumed to be a case of syphilis congenita tarda. "We found a series of syphilitic skulls in the Museum Dupuytren showing changes which were identical with those which we are able to demonstrate in the rœntgenograms of our patients" These hyperostoses "which in some instances had the aspect of large cauliflowers, were encountered in crania which externally did not show any changes at all"

PICARD (1926) reported a similar case, i e, that of a female aged 72 who was the subject of senile dementia and presented atrophy (825 g) and softening of the brain. The alteration was looked upon as "Paget-thickening."

In 1927 SCHREINER published a comprehensive paper on human bones found in the famous Oseberg ship, dating from the Norwegian iron age Two female skeletons were found in the ship. The skull of the older woman,

whose age was estimated at 50 years at least, or perhaps even between 60 and 70, presented a typical and fairly marked Hfi (Fig 99). SCHREINER reported in brief that he had encountered a similar alteration before in a woman aged 72. On the occasion of the demonstration in 1907 of the hyperostotic skull, HARBITZ reported 3 similar cases in women which were detected at the autopsy; two of these were nulliparæ We shall return to

was present, a condition frequently found in septic abortion Two cases were the subjects of ulcerous endocarditis. These younger women form a distinct group. Subsequently there was an interval of eleven years in DRESSLER's material of hyperostoses without post-mortem cases Out of the older women 10 were aged between 50 and 59, 20 between 60 and 69, 17 between 70 and 79 and 1 between 80 and 90. Seven men were aged between 47 and 70 years

on the part of the superposed bone" DRESSLER's microscopic examinations will be discussed later

To GREIG (1928) all credit is due for his comprehensive and important study of 188 museum specimens, out of which 32 (or 17 per cent) showed Hfi The alteration was commonest in women in advanced years (the ratio of males to females was 1·7). He states that the skulls of females

osteophytic growths from each side of the sagittal sulcus to the obliterated coronal suture. Anteriorly the osteophytes were more nodular; posteriorly they formed rather flattened bulgings and thickenings of the inner table. Out of the 28 females whose skulls were examples of Hfi, 2 were "very fat." Eleven cases were nulliparæ, 4 were uniparæ and 4 multiparæ. In 13 cases the data on pregnancy and so forth were missing. Psychically, 2 women were more or less insane during the last years of their life, the remaining 26 were normal According to GREIG the alteration of the skull cannot be brought into any appreciable relation either to the disease or to the cause of death of the patient.

Of the male cases reported in GREIG's paper the following are specially interesting and will later be discussed once more. In no case was the condition of the testes noted. Case 1. Male aged 77. The hyperostosis was flattened, smooth, rounded and dense. The diploe was well defined and in no way altered. The osteophytes had retained the compact character of the inner table of which they appeared to be an hypertrophy. Case 10, aged 60. Smooth osteophytic nodules were associated with several "excavations" in the inner table. In addition there was slight ossification of the tentorium. Case 17, aged 66 A slight osteophytic nodular growth was present on each side of the saggital sulcus at the level of the frontal tuberosities. Case 25, aged 66 The skull was the seat of chondrodystrophy and presented several anomalies on its base, particularly in the posterior part of the anterior skull groove

GREIG's conclusions can only be partly quoted · "In extreme cases hyperostosis results in diminution of the capacity of the skull; a possible atrophy of the brain may in all probability even stimulate its enlargement. The coexistence of acromegaly with hyperostosis is most likely incidental only." Some of his conclusions are as follows · (1) *Intracranial osteophytes are harmless and symptomless.*[1] (2) Intracranial osteophytes are concomitant with advancing years and always associated with absorption of calcium from the bones locally and/or generally. (3) *Intracranial osteophytes have no relation whatever to either syphilis or insanity.*[1] (4) There is no evidence that intracranial osteophytes are originated by child-bearing, and none that normal pregnancy or normal puerperium stimulates their development.

The merit of a very important contribution is due to STEWART (1938). In "the dementias of epilepsy and chronic insanity" a general thickening and sclerosis of the skull is said to be the most common anomaly STEWART classifies Hfi, "which seems to be a rare condition," into three types · (1) Two thick tabulæ and a normal diploe. (2) A thickened nodular or flat inner table. (3) Enlarged diploe between two thin tables

He reported 6 cases of frontal hyperostosis, Case 1. A female aged 62 (?) who was the subject of melancholia. She was "torpid and sluggish" as well as extremely fat, and finally developed polyuria The brain weighed 1,150 g [illegible] hypophysis was unusu[illegible] [illegible]nken and cirrhotic [illegible] "marked sclerosis, [illegible] [illegible]ngulation of the cells by tissue." The pars intermedia showed lymphatic tissue and proliferation of cells towards the posterior lobe, which otherwise did not show any alterations. Case 2. A female aged 63 suffering from "insanity with gross lesions" and dementia She was extremely fat and there was hair-growth on the upper lip and chin The brain weighed 1,245 g. Typical Hfi was present The sella turcica was enlarged and firm. The ovaries were

[1] Italicized by F. H.

atrophic. The capsule of the hypophysis was thickened. The anterior lobe was sclerotic and presented atrophy of the cells. Numerous eosinophils were present. Case 3 A female aged 73. She was suffering from "recurrent melancholia" and subsequently became insane She was extremely fat and had a beard and moustaches The brain weighed 1,160 g. The frontal bone presented typical alterations The hypophysis was slightly enlarged. The microscopical findings were identical with those reported in Cases 1 and 2 Case 4 This instance was a somewhat older museum specimen. There was no history Case 5 A male aged 46 who suffered from epilepsy and dementia He was fat and infantile, the skull was very thick There

obesity in the insane—and especially those of the female sex—seems to be too frequent to be merely accidental and, when considered in the light of the pathological changes in the three cases recorded above, gives grounds for believing that we are here dealing with a *hitherto undifferentiated type of dyspituitarism*"[1]

In 1928 HELLMER read a paper in which he discussed the radiological appearance of Hfi According to this author the alteration is fairly common. *In no case were there any symptoms which might have been brought in direct relation to hyperostosis.*[1]

In his paper on Hfi BERTOLOTTI (1929) advanced a new theory on the pathogenesis of this condition. He believed that chronic pansinusitis—which

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dominantly women of advanced years (aged between 64 and 93) On

[1] Italicized by F. H.

female, however (Case 15), was somewhat younger—50 years—and another female (Case 17) was even as young as 34 years. This case, however, was only clinically and radiologically examined. Most likely a severe endocrine disorder was present in this instance. According to the history, 5 out of 15 female cases were very fat, 3 were fat, and 4 were well fed or corresponded to the average standard. Three individuals seem to have been thin or very thin. The atrophy of the brain, which was presumably of the senile type in most of these cases, was in some of them very pronounced (1,010 to 1,030 g.) The brain of 3 of the old women weighed 1,200 g. In a couple

one place remnants of the normal hypophysis with its three parts were found." The thyroid gland was moderately enlarged and slightly nodular. Case 17. A female, single, aged 34. From the age of puberty she had developed adiposity which progressed. A roentgenogram of the skull taken when she was 24 years old revealed an apparently normal sella and Hfi in its initial stage She was fat (weight 80 kg.). Her breasts were poorly developed; pubic and axillary hair-growth was sparse. She suffered from temporary polyuria and glycosuria There was gradual accretion of the existing hyperostosis.

The cases reported by MOREL comprised, in addition to these 15 females, 2 male subjects The history of one of them—a man aged 62—is rather incomplete. The skull was fairly heavy, moderately thick and sclerotic; it presented exostoses on the frontal bone. The other was that of an insane person aged 42 who was very thin The brain weighed 1,200 g., the skull presented hyperostosis, especially on the frontal bone. The testes were completely fibrous

In the 4 cases on which Morel personally performed the post-mortems the hypophysis was of rather varying appearance In Case 1 Ac's predominated, whereas Bc's were but scantily represented. In Case 2 there was increased pigmentation of the neurohypophysis and sclerosis of the anterior lobe In Case 3 there were present "one or two round, small and well-defined accumulations" of Cc's The Ac's occupied the lateral part of the anterior lobe; the Cc's showed vacuolization. In Case 4 only Cc's and Bc's were present in considerable numbers, even in this case there was predominance of Ac's As to the condition of the hypophysis in Case 8, see above

Pathogenetically MOREL ascribed decisive local importance to the firmly

headaches) were rather inconstant; in some cases the direct symptoms were absent MOREL's considerations on the associated symptoms of "the tuber-infundibulum-hypophysis system" will be discussed later

calcifying and bone-forming pachymeningitis originating from the sinuses

REDAELLI (1931) reported 3 cases · Case 1. A male aged 81 who was senile and marantic and the subject of severe and typical Hfi (excellent plate). Case 2 was that of a female aged 41 suffering from psychosis and obesity. There was a very asymmetrical and perhaps otherwise even very atypical

series of endocrine and infundibulo-tuberal disorders *does not authorize the creation of a syndrome indicative of Hfi associated with adiposity*,[1] a statement which contradicts MOREL's theory. REDAELLI assumes that, as regards the pathogenesis, various general and local, mechanical and biological factors play a part in this process, viz, (1) shrinkage of the brain, (2) decubitus dorsalis causing backward displacement of the anterior brain pole, (3) disorder of calcium metabolism He rejects MOREL's traction theory.

SCHIFF and TRELLES (1932) described a case which they labelled "Stewart-Morel's syndrome of traumatic origin" A car-driver aged 60, after a motor accident, developed infundibulo-tuberal symptoms (adiposity, increased libido, psychical symptoms, epileptiform seizures). There was X-ray evidence of Hfi which, according to the authors, was secondary to the

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bee
and X-ray evidence of hyperostosis The patient is alive

NIEUWENHUIJSE (1933) published his autopsy experience on Hfi and reported the following cases as examples of this alteration Case 1 A female aged 83 with arteriosclerosis and dementia She died of heart and kidney insufficiency after having been bedridden for a prolonged period Typical Hfi was present and slight atrophy of the brain (1,100 g) The remaining portions of the skeleton were, with the exception of a slight spondylitis deformans, normal. As regards the endocrine organs there was nothing abnormal Case 2 A female aged 89 with arteriosclerosis and dementia died of a ruptured abdominal aneurysm after being bedridden for a prolonged period The post-mortem findings were identical with those reported in Case 1 Case 3 A female aged 63 who suffered from cancer of the uterus was bedridden for three weeks before her death In this instance the hyperostosis involved a much larger area and resembled, in the neighbourhood of

[1] Italicized by F H.

the middle meningeal artery, a mountainous landscape. . . . The branches of the arteries seemed to run through tunnels The brain was small (1,100 g.), the endocrine organs showed no pathological alterations NIEUWENHUIJSE states that he detected 14 examples of these alterations in 56 autopsies (it should be mentioned, though, that even slight or initial alterations were tabulated) and that they were exclusively present in female subjects of advanced age. When discussing the pathogenesis of this condition he quotes THOMAS' and JORES' investigations NIEUWENHUIJSE *does not find any appreciable connection between the clinical symptoms and the hyperostosis*;[1] neither does he support the view that the alteration is m

which he labelled as "compen- to a mechanism which, though ed to be the underlying cause.

MOREAU (1934) reported the case of a man aged 35 who died in 1786, which, in our opinion, is not a true case of Stewart-Morel's symptom; it is, therefore, not referred to in this survey.

According to STERTZ (1934) instances of this type were doubtless not examples of secondary hyperostosis, a condition encountered as sequel of atrophy of the brain, but cases of primary hypertrophy of the bone. STERTZ stated that Hfi will be understood if in accordance with G. HERMANN'S view it is assumed that there may exist a "directed brain pressure." The frontal outgrowths are apt to exercise an active pressure in the direction of the base of the brain

ERDHEIM (1935 and 1938) published papers on hyperostosis of the roof of the skull in which he dealt with "the generally recognized bulging bony hich are characteristic eant Hfi. The results

i and its significance and *stressed the great incidence of the condition, its frequent association with obes*

lect

Hfi

present the material was divided into three classes and, according to the type, into three groups, viz., "nodular," "sessile" and "mixed" alteration Seventy cases (97 2 per cent) were females, of the 2 male subjects 1 was

From the following table it will be clear that, as regards age distribution, MOORE's findings deviate from those of earlier publications —

Incidence by Decades of Persons with Hfi							
11 to 20	21 to 30	31 to 40	41 to 50	51 to 60	61 to 70	71 to 80	Total
2	11	15	16	20	5	3	72

[1] Italicized by F H.

Out of the 6 cases with most marked changes 2 occurred in the third, 2 in the fourth and 1 in the fifth decade; out of the 26 moderately pronounced examples 13, or one-half of the cases, occurred before the fiftieth year. Approximately 51 per cent. of the female subjects had been at least once pregnant. The presence of neurological or neuropsychological symptoms called for X-ray examination of the skull in 70 out of the 72 cases; the remaining 2 cases were traumatic cases. Forty-four per cent. of the cases were obese. From the [illegible] of the patients gave a long [illegible]. There is no evidence that [illegible]

[illegible] a definite syndrome which is distinctive. Polyphagia, polydipsia, polyuria and disturbance of sleep, emphasized as important symptoms by MOREL, were not recorded in 59 of the cases. Possibly these symptoms were so slight that they escaped notice."

MOORE's second paper is based on even more comprehensive material and comprises 6,650 non-insane living [illegible]

[illegible] divided into four types:—

1 *Nebula frontalis* [illegible] and [illegible] It [illegible]

3 [illegible] the [illegible] diffu[illegible]

4 [illegible]

In the 6,650 individuals who were X-rayed there were 229 positive cases. These were distributed in the following manner:—

Nebula frontalis	76
Hyperostosis diffusa	40
Hyperostosis frontoparietalis	17
Hyperostosis frontalis interna	96

This material [illegible] these presented diffu[illegible] Two hundred and [illegible] en. Out of 36 insan[illegible] ere women

Ir[illegible] MOORE found 40 cases

[illegible] frontalis	13
Hyperostosis diffusa	3
Hyperostosis frontalis interna	[illegible]

Out of these 660 [illegible] the men ar[illegible] otherwise [illegible]

¹ Italicized by F H

The histories of 193 cases of thickening of the skull were analysed It was found that the women who were the subject of obesity frequently showed hair-growth on the chin and less frequently on the upper lip. Further, the following symptoms were recorded: "headache . . . easy fatigue . . . muscular weakness; nervousness and a tendency to worry, and depression; dimness of vision and occasionally diplopia; epileptiform seizures; impairment of memory; mental slowness . . . dementia . . . dizziness; disturbance of equilibrium and gait; seventh-nerve weakness . . . speech difficulty, apparently motor . . . sensory disturbance . . . dragging of a lower extremity . . transitory hemiplegia and hemiparesis . . . general neuromuscular insufficiency. . ."

As regards the pathogenesis of the skull changes MOORE stated in his first paper: "Hyperostosis frontalis interna is the antithesis of those diseases which have a deficiency of skeletal calcium as a part of their picture. It is, therefore, a reasonable supposition that it is a disorder of the calcium metabolism in which that mineral is present in excess in the organism. GREIG and MOREL share this opinion There is associated a disturbance of fat metabolism manifested as obesity which is at times extreme. The occurrence of the latter is less constant than the calcium disorder, as it is seen in but 44 per cent. of the cases . . . Since hyperostosis frontalis interna occurs almost exclusively in women it is proposed that there is a special structure present in the female which governs the calcium metabolism essential for menstruation, gestation and lactation. These three functions require the assimilation and disposal of an enormous amount of calcium and the requirements are intermittent. Now, if such a theoretical mechanism should not undergo involution in step with that of the sex organs of the female of known function there might result an aberration in calcium metabolism This appears to take place in hyperostosis frontalis interna, the deviation from normal being the retention of calcium which should be eliminated. The involution of such a calcium control mechanism should be greater with advance in years In this condition, however, involution is not in equilibrium with that of ovary, uterus and breast; it may be that it is precocious, and hyperostosis frontalis interna a manifestation of premature old age"

In his second paper MOORE's statements were somewhat reserved: "The ultimate causation of calvarial hyperostosis and the accompanying clinical phenomena is conjectural but it is probable that there is a single factor [illegible] which [illegible] that [illegible] low basal metabolic rate, increase in sugar tolerance, serum calcium and phosphorus have shown no change, but the period of observation for this has been too limited The hyperostoses cannot be identified as a part of any of the bone dystrophies as they are at present known. Since the overwhelming majority of cases occur in the female, its separation from those diseases which have an equal or nearly equal distribution in the sexes is unnecessary. The hyperostoses and the associated phenomena cannot be identified as a feature of those disorders, which are restricted in their occurrence to women as such disorders are at present known. The roentgenographic incidence by sexes is 225 females and 4 males From this it appears that the condition must be due to a disorder of some structure peculiar to the female which is as yet unknown"

In his third paper MOORE chiefly dealt with the clinical picture of these cases The analysis of 36 cases from a sanatorium revealed "that there is a

symptom complex accompanying the osseous changes which is as characteristic as the rœntgen findings The symptom complexes of the several types (of hyperostosis of the skull) are closely allied and in the future they may be proved to be identical."

The symptomatology was *characterized by the more or less constant* association of the clinical disorders mentioned.

As regards the calvarial changes MOORE adds: "The fact that the hyperostoses coexist in the same persons and that the skulls are generally thickened in cases of all types sustains the view that, though morphologically distinct, all types have the same fundamental etiology, this is indicated also by the related clinical phenomena. . . The disorder at present cannot be considered as part of any of the endocrine diseases as such diseases are at present known. . . . The evidence is that the condition is a metabolic disease in which, as far as it is known at present, fat and calcium metabolism only are at fault."

The psychic symptoms can progress and end in dementia. Therefore MOORE recommends in such cases a surgical intervention "It appears that much good might be accomplished by turning down the frontal bone flap."

CARR's investigation (1936) is, to a certain degree, compatible with those of MOREL and MOORE CARR's material comprised 17 cases of nebula frontalis, *hyperostosis frontalis or hyperostosis calvariæ diffusa* *Concerning* symptomatology CARR tabulated his 17 cases as follows:—

	Per Cent		Per Cent.
Obesity . .	64 7	Headache . . .	82·3
Difficulties of memory	88 2	Weakness . .	58·8
Dizziness .	64 7	Visual disturbances .	41 1
Convulsive seizures	35 3	Menstrual disturbances	76·4
Mental changes	58 8		

CARR suggested as treatment the administration of "amino-acetic acid by feeding large quantities of gelatin daily."

In the discussion following CARR's lecture MORTIMER gave a brief survey of the skull changes in the presence of different endocrine disorders He reported the case of a female aged 18 years who was the subject of extreme obesity and presented general sclerosis of the roof of the skull, chiefly involving the pars frontalis "on the inner table of which there was well-marked formation of exostoses" MORTIMER emphasized the connection between pituitary disorders and calvarial changes "Thus, I have seen calvarial change in patients whose chief complaint was excessive growth, obesity, delayed maturity, premature senility or diabetes insipidus and . . . in cases of lesion of the central nervous system as well as in cases of clearcut Fröhlich syndrome and in cases of long-standing acromegaly"

ALMEIDO-TOLEDO (1936) reported a case of Hfi

EISEN (1936) reported a clinical case of Hfi in a female aged 45 years Originally she weighed 168 lbs, later on 150 lbs and was the subject of obesity, diabetes and hypertension

FRACASSI and MARELLI (1936) described 4 clinical cases Case 1. A male aged 40 complained of headache, thirst and vertigo Radiologically there was pronounced Hfi. Case 2 A female aged 24 with glaucoma, complained of frontal headaches Radiologically Hfi Case 3 A female aged 64 complaining of similar symptoms Hfi coexisted. Case 4 A female aged 35 complained of headache and vertigo; gradually progressing Hfi which was recognized in the X-ray

In the same year ESTAPÉ published a survey of research on hyperostoses.

GESCHICKTER and COPELAND (1936) briefly mentioned this alteration: "Hyperostoses of rounded or irregular contour resembling osteomas may project from the inner table of the skull in the anterior portion of the calvarium. The frontal and parietal bones are usually involved diffusely. According to YOLTON, this condition is observed more frequently in women than in men and is a compensation for atrophy of the brain. It is usually found only at autopsy in adults. The compact or spongy new bone projects inwardly from the inner table without any evidence of change in the outer table. Microscopically the new bone formation is similar to that in the [illegible]
and eburnated

HENSCHEN [illegible]
and obesity, in [illegible]
term, "Morgagni's Syndrome."

JAMES (1936) described the case of a woman aged 51 who was admitted to hospital as the result of a fall on her head. She was fat, in excellent condition, measured 152 cm. in height and weighed 95 kg She was irritable, bad-tempered and complained of headaches and depression. There was X-ray evidence of Hfi This author advised surgical intervention "when the hyperostosis gives rise to signs or symptoms of increased intracranial tension or to focal signs."

[illegible]

responsible for eliciting a compression symptom-complex, similar symptoms would also be observed occasionally in the presence of osteomas of spheno-occipital origin. . ." It is, therefore, not warranted to place the radiologically demonstrable osseus changes in the foreground of interest; "*The picture of the disease is conditioned rather by the degenerative senile alteration of the brain and most likely also of the hypophysis*" [1]

ABÉLY and DELMOND (1937) report a clinical case of Hfi associated with adenolipomatosis symmetrica and dementia.

DONINI (1937) published 3 cases Case 1. A female aged 65 presenting Hfi. At the age of 50 she developed sinusitis and adiposity. At the age of 59 she complained of impaired memory, difficulty of orientating herself [illegible]

[illegible] Case 3. A female aged 60 suffered [illegible]ression, dysarthria and headache. [illegible]*phy of the cerebral hemispheres*, [illegible] microscopically there were various senile changes in the brain

HENSCHEN (1937): "Morgagni's Syndrome" monograph

LEVISON (1937) reported 2 clinical cases of MS Case 1 A female aged 75 years who was very tall and fat, had a masculine appearance, but did not manifest any considerable hypertrichosis Her grandmother, a daughter of the patient as well as several of her numerous brothers and sisters showed gigantism of similar type. She complained of trigeminal neuralgia of seventeen years' standing; no other objective neurological or psychiatric symptoms were manifested There was X-ray evidence of Hfi. Case 2. A female aged 57 who measured 153 cm. in height and weighed 120 kg. presented

[1] Italicized by F H.

fairly abundant masculine hirsuties on the face. X-ray showed pronounced Hfi ; clinically she was depressed.

MOREL (1937) wrote : " It is no mere accident that hyperostosis is mainly encountered among the patients of lunatic asylums and neuropsychiatric clinics where the frequency of this condition seems to be greater than anywhere else." MOREL recommended, as treatment for the headache, decompression by means of a large frontal flap.

RASO, MS (1937).

SCHACHTER, MS (1937).

M. B. SCHMIDT (1937) described shortly Hfi in HENKE-LUBARSCH's handbook of pathology.

SOMOGY and BAK (1937) published two clinical cases : Case 1. A female

36 2° R. The basal metabolism was +1 per cent. Radiologically there was a mild Hfi ; the sella did not show any alterations. Psychically she suffered from depressive inhibitions and anxiety. The menses set in at the age of 9 years. When she was 13 she began to have attacks of megrim, and when she was 20 years old amputation of the uterus was performed. Case 2 A rather badly nourished female aged 52. Psychical trauma at the age of 30, followed by disorders of the nervous system She stated that for twelve years she had suffered continuously from headaches, weakness and various *vague complaints. The blood pressure was 155/110. There was* X-ray evidence of Hfi.

CANAVAN (1938) performed 3,250 post-mortems on insane subjects and found 230 examples of Hfi (7 per cent) He writes : " *The lesion seems to have no constantly associated pathological change. Patients with exostoses rarely are recorded as complaining of subjective symptoms such as fullness, headache or a feeling of heaviness or pressure in the head.*" [1]

DELMAS-MARSALET (1938) Clinical case : A female aged 52 who thirteen years ago had an operation for otitis and mastoiditis and complained subsequently of severe ir

ectomy. She was very fa

system. She exhibited

of Hfi.

FATTOWICH (1938) reported 3 cases Case 1. A female aged 71 who

The post-mortem revealed the following . Height, 150 cm., weight, 130 kg , presence of Hfi , the investigation of the pituitary gland showed " hypophysitis chronica interstitialis productiva " Case 3 A female aged 46 who in 1932 weighed 66 kg and in 1938 116 kg. There was psychical depression and X-ray evidence of Hfi

FELDAM and SALONEY (1938) published a paper on the syndrome of Hfi

[1] Italicized by F. H.

In a discussion following a lecture on brain atrophy he stated his views on the relation

LEHOCZKY a

was small and c

Her appearance

the blood pressure was 180/110. She had inverted sleep rhythm, extremely severe headaches There was

se of a female aged 37, with hysteria, weighing 96 kg. There was X-ray evidence of Hfi. Arteriographic examination showed no signs of pre-existing brain atrophy; the coexisting Hfi would have been capable of exerting marked pressure on the brain. According to MONIZ this compression could have furnished the explanation of part of the secondary symptomatology.

NEGRI (1938) described a case of MS.

PERKINS and BIGLAN (1938) reviewed the literature on the Stewart-Morel's syndrome and reported a clinical case.

RADEMAKER (1938) described 5 clinical cases in women: Case 1. The

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ng

revealed a typical Hfi and clearly flattened gyri. The outgrowths on the inner side of the frontal bone were removed and the bone flap was replaced. The operation resulted in "considerable amelioration." Case 2 was that of a fat individual aged 40 who had a thick beard. She was subject to attacks

There was X-ray evidence

and presented progressive

the face and appreciable

eakness and ataxia. There

ged 41 presenting adiposity

of the breasts, the abdomen and the nates She complained of headache and vomiting. There was X-ray evidence of Hfi. Case 5. This individual was aged 32 years and complained of headache and vomiting; the X-ray showed Hfi.

REIDER (1938) reported 2 cases · Case 1. A female aged 55 years. She had never been pregnant. When she was 33 hysterectomy was performed. At the age of 52 she began to complain of fatigue and nervousness. Previously

pressure of the hyperostoses The wall of the third ventricle showed in this

mortem revealed atrophic ovaries and Hfi + + +. The hypophysis showed

Bc hyperplasia The microscopical examination of the brain was negative
-trophic sclerotic
not described
In both cases
with excessive

ROGER (1938) described 2 clinical cases · Case 1. A female aged 57 was the mother of eight children. She weighed 157 lbs. and complained of headache and insomnia There was X-ray evidence of an early Hfi. Case 2. A female aged 52 who had five children and weighed 220 lbs She was obese (of the pituitary type) and complained of headache Considerable Hfi was present.

SALZER (1938) published a paper on "the frontal hyperostosis syndrome."

SAMSON (1938) contributed a paper on Hfi

VAN STEENBERGEN VAN DER NORDAA (1938) described 5 clinical cases and 1 case on which a post-mortem was performed · Case 1 A female aged 26 complained of attacks of vomiting and spells of unconsciousness and headache. She weighed 53 kg. There was X-ray evidence of Hfi. Case 2. A thin female aged 66 with moustaches, suffered from Alzheimer's disease. Hfi was present in the X-ray. Case 3. An acromegalic female aged 71 weighing 85 kg and presenting somewhat masculine hirsuties and X-ray evidence of Hfi. Case 4. A female aged 53 showing masculine hirsuties and weighing 108 kg There was X-ray evidence of Hfi but no objective neurological symptoms. Case 5 was that of a woman aged 38 presenting masculine hirsuties and scanty pubic hair. She weighed 86·5 kg. Amenorrhœa for six years. The X-ray examination revealed pronounced Hfi and a large sella Case 6 came to autopsy A female aged 75 weighing 100 kg was the subject of arteriosclerotic dementia. The blood pressure was 220/95 There was hæmorrhage of the brain and Hfi The authors expressed their opinion as follows: "*The syndrome of Morgagni may develop without any complaints, but in its very nature is often accompanied by the incommodities of old age*" [1]

TROELL (1938) described 2
thyrotoxicosis: Case 1. A fem
sella (19 × 11 mm.). She died
weighed 7 g. and contained a l
suffered from acromegaly for te

BARTELHEIMER (1939-42).
who, though married for three

Morgagni triad and diabetes refractory to insulin appears to me to be of
essential and maj
severe frontal he
menses were norr
and Hfi. There
strongly suggesti

[1] Italicized by F. H.

assumption that there exists a close relationship between internal frontal hyperostosis and diabetes of the pituitary type is fully justified."

DE FRANCO (1939) described 2 cases of lues associated with Hfi. The coexistence of lues with Hfi is not merely incidental. According to this author it is highly probable that lues may give rise to this typical process

FUMAROLA (1939). According to this author a more or less diffuse thickening of the vault of the skull, particularly in the shape of Hfi, is "occasionally" found in patients complaining of intractable headache, but otherwise not manifesting any objective symptoms. On the other hand, Hfi is frequently encountered in individuals who had never suffered from headache "*The series of cases in which permanent disorders were absent in spite of the presence of considerable endocraniosis is too great.*"[1]

GOLLAN (1939) reported a case of Hfi.

HENSCHEN (1939) published a class[illegible]
According to this author, at least three [illegible]
calvarium may be distinguished, viz. (1) [illegible]
hyperostosis in rickets, osteitis deformans, syphilis and meningoma, which might perhaps be designated *dysostotic* or *osteitic*. (3) *The hormonally conditioned*[1] (a) puerperal osteophytes, (b) Morgagni's frontal hyperostosis, (c) hyperostosis in acromegaly Transitional and combined forms undoubtedly occur between the different sub-groups in Group 3.

KORPASSY (1939) reported 5 cases of Hfi on which autopsy was performed All these instances were old and fat women. None of them presented virilism *The symptoms described by neurologists were absent in these 5 cases.*[1] The syndrome suggests a disease of the ovaries and the hypophysis; the endocrine glands did not show any essential changes.

LUCHERINI (1939) published 8 clinical cases and 3 cases that went to autopsy. The latter were. Case 1. A female aged 66. Blood pressure, 180; suffered from diabetes and an abdominal malignant tumour. The post mortem revealed Hfi + + + Case 8 A female aged 75 whose blood pressure [illegible] rain Hfi + + + was found at autopsy. [illegible] ating dyspnœa and œdema. Hfi + + + [illegible] which no post-mortem was performed were Case 2. A female aged 68 suffered from lues The blood pressure was 180 There was X-ray evidence of Hfi Case 3. A female aged 47 who complained of pressure localized to the supraorbital region Objectively there was nothing noteworthy. Blood pressure, 190 X-ray showed Hfi. Case 4 A female aged 57 complained of headache. Blood pressure, 205 X-ray showed mild Hfi. C[illegible] and vertigo Objectively [illegible] worthy Blood pressure, 1[illegible] A female aged 75 who suffered from headaches, dyspnœa and glycosuria Blood pressure, 175. There was X-ray evidence of Hfi Case 10. A female aged 79 complained of weakness and showed tremor Encephalographic examination revealed cerebral atrophy Blood pressure, 230 There was X-ray evidence of Hfi. Case 11. A female aged 67 complained of pressure localized to the precordial region Blood pressure, 200 There was X-ray evidence of Hfi. Case 7. A man aged 67 He was of the eunuchoid type, [illegible] there was atrophy of the testes [illegible] and general weakness. Blood [illegible] Hfi According to LUCHERINI [illegible] *ses in the absence of endocrine* [illegible] *e of minor importance (such as*

[1] Italicized by F. H.

headache, vertigo) and which most likely are accompaniments of the advanced years of the patients, of cerebral arteriosclerosis and of hypertension.[1]

RICHTER (1939) examined in Cologne 1,227 X-rays of skulls taken within the past eight years. Out of these 377 were women and 850 men (31 and 69 per cent respectively). Ninety-three cases (or 7 6 per cent.) were examples of Hfi, of which 81 per cent were females and 19 per cent. males. In the

that these complaints were caused by mechanical pressure on the brain. Their underlying cause most likely was a disturbance of endogenous regulation, a disorder which, in all probability, is identical with that responsible for the *formation of hyperostoses. Nowadays clinicians decidedly reject the* assumption that Hfi exerts any strong pressure on the brain or causes distortion of the hypophysis

ROGER, SCHACHTER and BOURDOURESQUES (1939) published a paper on MS

SOTO (1939) stated that in the presence of acromegaly the hyperostotic growths involve the entire calvaria.

TAGER, SHELTON and MATZEN (1939) published a paper on hyperostosis calvariæ interna and its clinical significance.

TRELLES and MENDEZ (1939) described 4 clinical cases in which Hfi was radiologically recognized. All the cases were females aged between 32 and 62 years The irregularity of the occurrence of the psychiatric deficiency symptoms is striking. The younger patients particularly manifested practically none. Certain characteristic manifestations were mostly demonstrable in women of advanced age. At the final stage confusion was present similar to senile dementia

SZABLOCS (1939) proposed an adequate modification of HENSCHEN's classification of hyperostoses of the skull, and established the following pathogenetic types · (1) *compensatory*, (2) *hormonal*, (3) *dysostotic*, (4) *irrilative hyperostoses*[1] On the basis of this classification LESZLER (see p 26) published in 1940 a survey of the pertinent radiology

BELLONI (1940) described one clinical case The striking features of the clinical history were giddiness and Hfi which was radiologically demonstrable only later on.

BOTHELO (1940).

ELDRIDGE and HOLM (1940) stated . " Out of 200 insane women aged between 23 and 87 years, 50 (or 25 per cent) were radiologically definite cases *It is impossible for us to concur in the opinion that a definite syndrome, sometimes referred to as the 'triad of Morel,' is present in cases of localized hyperostosis of the frontal bone* , at least, so far as the female population of a mental hospital is concerned *the occurrence of Hfi does not have any close or significant relationship to any one particular mental disease* "[1]

HEMPHILL and STENGEL (1940) reported 2 cases of MS which they thought to be the first observed in mother and daughter (DONINI's was the first) A 65-years-old patient with Hfi presented a diffuse and focal loss of ganglion cells of the third, fifth and sixth cortical layers in the frontal and parietal lobes

[1] Italicized by F H

LESZLER (1940) published 3 clinical cases: Case 1 was that of a woman aged 31 who, after the first childbirth ... [illegible] ied 11 kg. in weight and [illegible] ... ly evidence of Hfi. Case [illegible]

[illegible] ... of the skull and [illegible] ... A female aged 38 who for one year and a half suffered from giddiness, headache, vomiting and failing vision. She showed choked disc with hæmorrhages. There was X-ray evidence of Hfi; the sella was extremely dilated, the base was atrophied, the dorsum destroyed and a pituitary tumour was di[illegible]

[illegible] ... which he summarized his investigations covering a period of many years and concerning MS, particularly its presumptive neuropsychiatric symptomat[illegible] ... PENDE it is not yet possible to ascri[illegible] ... the patients to Hfi, "but it is, in all [illegible] ... the symptoms at least may be assumed to be due to [illegible] ... ction which the endocr[illegible] ... the diencephalo- [illegible] ... tion the existence

[illegible] ... BOURDOURESQUES (1940) reported a case of MS in a melancholic woman

ROSSIER and SECRETAN (1940) published in tabular form 35 clinical cases in which the presence of Hfi was radiologically diagnosed; 33 of these were females. Case 1. A female aged 55 suffered from insomnia and presented Hfi++. Case 3 A female aged 24 who four years ago developed encephalitis, as a sequel of which severe headaches set in She was stoutish Blood pressure, 170/80, and there was Hfi++. Case 5 A female aged 40 presented a symptomless Hfi++ Case 6. A stoutish female aged 38 had hypertrichosis and mild Hfi. Case 8. A female aged 52 who complained of intractable headaches and presented hyperostosis calvariæ and mild Hfi Case 9 A female aged 34 who [illegible] encephalitis now showed Parkinsonism and [illegible] 160/90. Hfi++ was present Case 10 [illegible] insomnia Blood pressure, 170/100 There was Hfi+++ Case 11 A female aged 41 suffering from extremely severe headache and insomnia after poliomyelitis was very fat and presented Hfi+++. Case 12 A girl aged 17 suffered from epileptic convulsions and extremely severe headaches She was not fat Hfi was present Case 15 A female aged 43 had been operated on for maxillary sinusitis Since childhood she had suffered from headache. Hfi was present Case 16 A female aged 31 who had had poliomyelitis was troubled with severe headaches since childhood. She was not fat. Blood pressure, 135/80 Hfi was present Case 17. A stoutish female aged 56 suffered from headache and hypertension Blood pressure, 245/100. Hfi+++ was present. Case 18 A female aged 44 suffered since childhood from extremely severe headache She was not stout. Hypertrichosis, epilepsy and Hfi+++ were present Case 19. A female aged 36 was subject to insomnia and extremely [illegible] childhood [illegible]

[illegible] ... was present Case 23 A female

aged 38 c
Case 24.
Hfi + + +
twelve y
Blood pre
since childhood from extremely severe headaches and presented a glioma of the occipital lobe. Blood pressure, 205/100. Hfi was present. Case 28. A female aged 69 No history of symptoms Hcd and mild Hfi were present. Case 30. A female aged 44 who was not stout complained of extremely severe headaches. Blood pressure, 220/170. Hfi + + + was present. Case 31. A female aged 62. There was no history of symptoms Hcd and Hfi were present Case 32. A female aged 40. She was not fat and presented Hfi + +. Blood pressure, 170/100. Case 33 A female aged 43 Very fat; suffered since childhood from severe headache and manifested epilepsy and early Hfi. Case
and presented r
any special syr
somewhat fat, complained of extremely severe headaches of one year's standing. Hcd and mild Hfi were present. Case 37. A female aged 36 suffered from severe headache and insomnia. She was not fat. Blood pressure, 120/80. Hfi + + was present. Case 38 A female aged 68 complained of extremely severe headaches and insomnia Blood pressure, 156/100. Hcd and mild Hfi were present. Case 39 A female aged 40 suffered from extremely severe headaches; she was operated on for maxillary sinusitis. Hfi + + was present. In addition, 2 cases of this condition in male subjects are reported of which one was that of a man aged 44 who was somewhat stout and complained of extremely severe headaches. Blood pressure, 130/70 Mild Hfi was present. Case 29. A man aged 62. He was somewhat stout Severe headaches troubled him since childhood. He suffered from insomnia and his blood pressure was 175/110 Hfi was present

In addition to these cases, ROSSIER and SECRETAN reported 6 (?) cases which came to autopsy. They were treated for entirely different diseases. According to the authors the case-histories did not contain much of interest. In five instances a cerebral atrophy was present The hypophysis did not show any noteworthy alterations

TANTURRI (1940) reported a case of Hfi associated with vertigo

BARCIA and CAUBARRERE (1941) contributed a paper on the alterations on the inner surface of the skull and their relation to radiology

GILBERT (1941) presented a paper on the syndrome of Hfi

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twent
was a
there
the se
anxiety but no objective neurological symptoms The blood pressure was normal, blood sugar 165, blood cholesterol 200 The author discusses the possibility of a chromophobe adenoma of the pituitary

KIAER (1941) reported 4 clinical cases Case 1 A female aged 29 had never menstruated She was small, rather infantile and presented hypoplastic breasts She was fairly stout and had rather pronounced moustaches. Radiologically she showed Hfi Treatment by ovex resulted in slight amelioration of her condition Case 2. A female aged 23 had normal menses She was tall and vigorous. Her voice was somewhat hoarse Masculine

hirsutism was present. She was very fat (116 kg.). There was X-ray evid-
of Hfi. Case 3. A female
was feminine
increasing head
aged 28 presented body structure and pronounced virile hair-growth.
She gave a history of headaches of one year's standing. There was X-ray
evidence of Hfi. As regards the neurological symptoms KIAER assumed
that Hfi, though partly furnishing an expl-

and typical
ataxia, loss of mem
female aged 45 sh obesity, hirsutism, polyuria. Blood pressure,
192/134. No typical Hfi was present. Case 3. A female aged 26 gave a
history of recent and sudden increase in weight, recurrent vertigo and
headaches. Early Hfi was present Case 4. A female aged 41 showed male
hirsutism, moderate obesity, typical Hfi. At the age of 37 unilateral ovari-
ectomy was performed, which was followed by mild menopause syndrome
Case 5. A male aged 19, the son of Case 4, manifested slight roughening of
the inner table of the frontal bone He did not have any complaints. Case
6 A girl aged 16, daughter of Case 4, manifested rather advanced Hfi and
mild hypothyroidism. Case 7 A boy aged 13 who
The
8
w
n acromegalic changes At the age of 42 artificial
menopause She showed diffuse thickening of the
Case 10.
of compla
no sympt
fication o complained of headache, depression and loss of
memory Case 13 A female aged 60 exhibited obesity, nebula frontalis,
slight Hfi and complained of headache. Case 14 An obese female aged 53
showed frontal headache and progressive Hfi. The presence of a brain
tumour was suspected Case 15 A female age 31 had sustained a motor
accident and showed pronounced Hfi
by any complaints. Case 16 A fem
showed incipient Hfi Case 17 A
There was pronounced Hfi Case 18 A female

female aged
vertigo, weakness, staggering gait, tinnitus, periods of
dizziness Massive Hfi and calcification of falx cerebri Case 22. A female
aged 33 years who suffered from recurrent headache. Three years ago
unilateral ovariectomy was performed Mild Hfi was present. Case 23 A
female aged 62 had a thyroid carcinoma, Hfi and a metastatic
of the skull Case 24
followed by nausea, vo
Hfi were present Ca
obesity and Hfi Sh

Case 26. A male aged 37 gave a history of recurrent severe occipital headache; mastoidectomy had been performed eleven years ago. Moderate Hfi was present. Case 27. A female aged 42 complained of progressive pain at the vertex, tinnitus, vertigo and failing vision She was found to have a temporal osteoma which was surgically removed. Hfi was present. Case 28. A female. She was moderately obese. For fifteen years she had been troubled by weakness There was polydipsia, polyuria, occasional glycosuria, multiple myelomata and moderate Hfi.

In view of the younger ages of detection of the Hfi reported in occasional papers on the subject and the 5 cases in this paper under 20 years of age, or 8 under
long preced
been report
A similar d
by the now not inconsiderable number of male cases reported in the literature, including the 5 of the above series. It is difficult, however, not to accord

HENSCHEN, but so far as KNIES and LE FEVER were aware their cases constituted the first evidence of such a background for the disease itself.

The discovery of well-marked Hfi in traumatic cases without previous symptoms suggests a long period of latency. KNIES and LE FEVER have been unable to classify the X-ray appearances in the manner of MOORE, and often could not escape placing a given case in two groups Thus of 28 cases, 23 showed Type I. intracranial changes alone or principally, but 4 others showed it in lesser form, secondary to more marked changes of another type Preradiological diagnosis was attempted in several instances, and was occasionally correct as shown by later pictures This is in agreement with the experience of ROGERS.

MCGAVACK and REINSTEIN (1941). A female aged 40, the mother of two children. Within four years she gained in weight from 65 to 94 kg. There was hair-growth on the chin, mild microcephalia, dorsal kyphosis, brachydactylia of the hands and feet and polydactylism of the hands. Blood pressure, 178/80 There was X-ray evidence of Hfi.

MOLLARET, MOLLARET and LE BEAU (1941). A woman aged 60. For seven years more and more frequent parietal headaches, in the following years intermittent visual disturbances, six months later typical epileptic fits. The patient was not fat but showed marked hair anomalies slight baldness combined with moustaches and hairiness of the limbs There were severe neurological symptoms loss of memory, diminution of the visual fields, difficulties in walking Radiologically there was marked Hfi and a general dilatation of the brain ventricles with atrophy of the brain cortex. A surgical intervention was performed, the right frontotemporal bone being trephined The bone was very thick and compact and brain atrophy was present During the next four years a slight amelioration of the condition was observed. The authors suppose a rather diffuse encephalopathy with slow evolution

MONTMOLLIN observed (1941) in MOREL's clinic 2 cases Case I. A woman aged 81 rather thin before menopause, afterwards pretty stout. Nine years before death thyroidectomy was performed. For many years frequent

headaches. In the last few years, particularly in the last months, marked loss in weight. For two to three months increasing psychical disorientation, nocturnal agitation and insomnia. The patient was a cachectic old woman with numerous cutaneous and subcutaneous tumours of various size and character Blood pressure 150/50, blood cholesterol 185. She died of pneumonia At the section there was a rather marked Hfi, but no brain atrophy. Case 2. The daughter of Case 1, aged 54. For a long time past she had suffered from frontal and retro-orbital headaches She was depressed, anxious and sleepless since her mother's death The patient was not fat, and she had numerous skin tumours like her mother. Clinically there was nothing of interest, the blood pressure was 125/50, blood calcium 90, blood phosphorus 41 5, blood cholesterol 277. Radiologically there was an Hfi. The autonomy of MOREL's syndrome is indubitable, and is also attested by the heredity. The coincidence of the syndrome and multiple skin tumours indicates " une ectomesodermose à déclanchement neuroendocrinien."

PETIT-DUTAILLIS, MESSIMY, RIBADEAU-DUMAS and TORRE (1941) published a case of Hed and Hfi in a man aged 50 with psychic disorders which improved after trepanation but returned after ten years; no progress of the cranial changes in this time

ROTH (1941) published 8 cases of Hfi. " In the series of the cases here presented *it was felt that the neuropsychiatric signs and symptoms were not to be attributed to the effect of the hyperostoses on the underlying brain tissue, but were the result of other factors,*[1] such as cerebral arteriosclerosis, hypertension, etc " ROTH advanced a personal theory on the pathogenesis of Hfi, to which we will return later

STEWART (1941) described an autopsy case. A female aged 68 had been insane for twenty-eight years. She was obese and hirsute. Her height was 152 cm., and she weighed 81 6 kg. Blood pressure, 165/90. Three years previous to her death she developed hemiplegia Autopsy: pronounced arteriosclerosis , hypertrophy of the left side of the heart , the roof of the skull was thick (522 g.); massive and bulging Hfi, some nodules on the inner aspect of the temporal bone and in the middle grooves of the skull; extreme atrophy of the brain (840 g) . right hemisphere 253 g , left hemisphere 465 g

TITCHE (1941) published a paper on Hfi

WILLIAMS (1941) contributed a preliminary report on hyperostosis of the calvaria.

ANDERSEN (1942) discussed 3 cases previously described by KIAER and reported a fresh case A female aged 25 presented a beard, masculine pubic hair and complained of headache There was X-ray evidence of Hfi. According to ANDERSEN the Hfi is by no means of infrequent occurrence, and in young women it is a very severe endocrine disease.

ANDREWS (1942). A woman aged 45 who was the mother of ten living children was the subject of " narcoleptic attacks," diabetes, severe frontal headaches She weighed 74·4 kg , her blood pressure was 160/80. The blood sugar during the attacks was 130 mg. per cent., the glucose tolerance curve between the attacks was on fasting 150 mg per cent , after one hour 210 mg. per cent , after two and a half hours 190 mg. per cent " *Radiological*

severe headaches and insomnia She manifested virilism, adiposity, hypertension (220), diabetes mellitus and radiologically Hfi

JACOBSEN and NIELSEN (1942) reported 10 clinical cases and 2 autopsy cases ; in all of them Hfi was recognized radiologically. Case 1. A female aged 42 weighing 118 kg. There was hypertension (230) and attacks of

female aged 57 with ... lly confused and demented. Case ... vertigo and psychic troubles. Ca ... eadache and fatigue Case 11. A ... sion of three years' standing and loss of weight. She was an example of steeple skull Of 2 cases which came to autopsy, 1 was a woman aged 64 exhibiting psychic disorders. At autopsy Hfi was found. The other, a female aged 64, presented hypertension (210/140) and died of apoplexy. The autopsy findings were atrophy of the brain, cerebral softening, Hfi. Summing up their observations the authors stated "Since hypertonia and arteriosclerosis were frequently manifested, *it is difficult to determine whether the symptoms were referable to psychic disorders and organic diseases of the brain, to arteriosclerosis and senility or to the existing hyperostoses* [1] The authors do not, therefore, deduce any conclusions from their material.

KIRK (1942) A female aged 25 who at school was already subject to spells of fainting Her intelligence was poor She exhibited virilism, adiposity and pronounced Hfi in the X-ray.

MELLGREN (1942), on the occasion of an investigation on the pathology of the hypophysis in the presence of interrenalism, reported 2 cases of Stewart-Morel's syndrome Case 7. A female aged 60 years showed adiposity, masculine hair-growth on the face and Hfi Within the past six years she had developed progressive cerebral troubles She died of pulmonary embolism. Autopsy findings Slight compression of the frontal poles caused by the Hfi ; a cystic angioblastoma localized to the cerebellum the size of a hen's egg. Case 8 A female aged 75 presenting adiposity, moustaches and Hfi Within the past three months there was onset of vertigo, staggering gait, intention tremor, nystagmus She died of pulmonary embolism The autopsy findings were A rather severe affection of the cerebellum of the degenerative and involutional type resembling senile involution.

In 1942 I MEYER published a case of marked Hfi combined with sclerosis of the calvaria in a cachectic woman 71 years of age with a malignant luteinoma of the left ovary. There was a marked virilism with male hairiness of the face and baldness since eight years previously The number of the Cc's of the pituitary was very reduced Ac, and particularly Bc, dominated entirely,

An Ac hypophyseal adenoma was suspected, but acromegaly was not definitely recognized Case 3 A female aged 40 years with extremely pronounced

[1] Italicized by F. H.

eunuchoidism. The author advances the view that Hfi should be considered rather as an endocrine symptom coexisting with hirsutism and adiposity

PETIT-DUTAILLIS, MESSIMY, RIBADEAU-DUMAS and XAMBEU (1942). A man with diffuse endocraniosis, Hfi and marked psychical disturbances (melancholia, mutism, negativism, catalepsy) was trephined in the left frontal region. Immediately following the operation his psychical state altered and after a period of four weeks with maniacal symptoms he was practically normal. According to the authors the improvement was due to the removal of the bone pressure on the frontal lobes.

RUBINO (1942) described a chiasmatic syndrome associated with Morgagni's hyperostotic "endocraniosis."

RUCH (1942) reported a case of Hfi accompanying pregnancy. The original paper was not available.

SAMSON, CARON and MARTIN (1942) published a paper on familial Hfi

The comprehensive monograph published by CAMPOS ("El Sindrome de Morgagni," 1943) included 12 clinical cases of Hfi. Case 1. A female aged 53 who since childhood was fat. Eight years ago she weighed 187 kg., in the clinic he
symptor
aches.
Case 1,
diabetes,
of Case 1 hyper-
tension. fat
female ag ved
incomplet of
Case 4. She was aged 63 and was moderately fat (86 kg.). No neuro-psychiatric symptoms, no diabetes. Hcd and Hfi were present. Case 6. A *fat female aged 60 had increase of intracranial pressure and Hfi.* *Case 7.* A female aged 30 had been acromegaloid since her two pregnancies Her height was 157 cm. and she weighed 100 kg There was pronounced virilism, no

HOLTEN (1943). A man manifesting neurasthenia, palpitation of the heart, a low blood pressure (95/70 to 105/80), frontal headache and radiologically pronounced Hfi.

LOUW'S paper (1943) does not contain case reports He claims that all future investigations should be based on cranial dysplasia as this abnormality is fairly constant.

NIEDNER (1943) encountered "a fully and beautifully" pronounced case of Hfi in two female patients who did not present adiposity or hirsutism; on the contrary, they were slender and graceful and were so young in years that they could not be considered as cases of MS. Case 1. A girl aged 16 presenting moderate post-puberty thyroidosis. Case 2. A young girl who, with the exception of diabetes, did not manifest any clinical endocrinological symptoms.

PEREIRA SILVA and D'ALEMBERT (1943). Case report.

SCHNITMAN and GERTZENSTEIN (1943) (quoted from CAMPOS' paper) reported 14 clinical cases, 13 of which were females and a boy aged 6. All women were fat: 5 of these manifested hirsutism, 5 were hypertensive, 7 complained of headache, 6 suffered from disorder of the carbohydrate metabolism In 5 cases the specific dynamic action of the proteins was subnormal, in 1 case it was elevated. In 2 cases the basal metabolism rate was elevated. In 4 cases endocrine treatment resulted in improvement.

BRAUNS (1944). Case report

FAUVETY (1944). Case report

MASCHERONI, REUSSI and MILLI (1944). Report of MS in two sisters with obesity and headaches

M. T. MOORE (1944) examined a woman aged 39 with calvarial hyperostosis and metabolic, endocrine and neuropsychiatric disturbances. Pneumo-encephalographical studies showed evidence of frontoparietal cortical atrophy, atrophy of the islands of Reil, asymmetry of the lateral ventricles and moderate internal hydrocephalus. "This syndrome may be readily confused with other endocrine or neuropsychiatric disorders, especially psychoneuroses, dementia paralytica, multiple sclerosis and tumour of the brain. It is important, therefore, not to fall into the error [illegible]

[illegible]

Th[illegible]

[illegible]

uncle of one of the patients, an insane person, revealed the existence of the disease. The symptoms are protean and variable and "consist of metabolic, endocrine, hypertensive and neuropsychiatric manifestations. Although only one of these general groups of symptoms may be predominant in any individual case, there are usually manifestations of at least two or more of them" In this series the symptomatology was the following :—

[illegible]	14 cases.
[illegible]	13 „
[illegible]	8 „
[illegible]	5 „
[illegible]	1 „

The principal metabolic disturbance was obesity. Hirsutism was encountered in 12 cases. When fat and hypertensive these patients might

however, that the disease does represent a definite entity, which, when taken in conjunction with the specific X-ray findings, may be differentiated as a distinct disease process." The symptoms would lead one to assume that the basic disorder of the syndrome is in the hypothalamic area of the brain.

OLDBERG discussed in a paper on senile diabetes and craniodysplasia (1944) the questions bearing on MS He based his considerations on the papers published by BARTELHEIMER, HENSCHEN, MOORE and MORTIMER, and investigated systematically the skull changes in 140 females who developed diabetes in the fourth decade In 20 (7 per cent.) of these cases a statistically significant dysplasia of the skull was present. The frequency both of dysplasia and hypertension was appreciably greater in these cases.

V SCHMIDT demonstrated (1944) Hfi in 20 out of 30 women with beards (average age, 78 years). Of 30 beardless controls in the same age only 3 had Hfi. Fourteen of the 20 hyperostosis patients were adipose, and thus had the classical MS. Except perhaps in one case, no connection between the Hfi and symptoms originating from the central nervous system was demonstrated. On the other hand, hypertension, cholelithiasis, osteoarthritis and hemiparesis were often found, which is ascribed to the obesity of these patients No relation to other diseases was found, especially none to endocrine disturbances. Clinically the syndrome is considered as a usually insignificant disease, a slightly abnormal variant of the usual post-climacteric change in the endocrine balance of womankind.

SUAREZ (1944). Case report

ALLISSON, BERTHOUD and BRANTMAY (1945) A case of acromegaly combined with Hfi in a woman, observed during fourteen years

HENSCHEN (1945) published a survey of the biology of the skull, giving special consideration to the senile changes, which will be discussed later in the present book.

DI LASCIO (1945). Clinical study of Hfi.

MASCHERONI, REUSSI and ITURBE (1945). A case of MS associated with headaches and variations of lumbar and sacral vertebral articular tropism.

MELLGREN (1945) published a comprehensive paper on "The Anterior Pituitary in Hyperfunction of the Adrenal Cortex," in which he studied the pathogenesis of the adrenogenital and menopausal syndromes and of prostatic hypertrophy He devoted
pituitary alterations in the presence
anterior pituitary lobe shows on the
Cushing's disease, adrenal virilism, MS
hypertrophy, "namely, an increase
hypertrophic amphophiles together with a less constant relative increase of the number of sparsely granulated basophiles", this being the expression

FEIRING (1946). An obese man aged 29 with MS and gout A common

pathogenesis was not demonstrable, the association of two diseases was purely coincidental.

LARUE, SAMSON and PATRY (1946). Case of Hfi.

VILA (1946). Cases of Hfi in diabetics.

During the proof-reading two important contributions to the present problems came to the author's notice. Unfortunately it was not possible to pay due regard to these papers in the present account.

PEDERSEN (1947) published a critical survey of the present problems from a clinical point of view, founded on the study of roentgenograms from 908 patients, 485 of whom constituted a normal material. "As a result of

[illegible]

It may be interpreted as a Morgagni syndrome (or parts thereof) in neuropsychiatric patients."

"In a few respects the writer cannot share HENSCHEN'S views. This applies primarily to the Morgagni triad which is of no particular significance. The essential thing is that a correlation exists between hyperostosis and adiposity and between hyperostosis and hypertrichosis. Hyperostoses—including Hfi—occur at a far younger age than assumed by HENSCHEN, but of course a pathologist does not see these patients"

WISSENBERG (1947) collected 60 clinical cases of Hfi, among them 2 males. The age of the women was in 13 cases 26 to 46 years, in 45 cases 47 to 81 years; the male cases were 52 and 72 years old In 14 cases there was a [illegible] Hfi were not included, [illegible] ns immediately to be [illegible] s of cranial changes." [illegible] A complete MS was found only in 8 cases, "but the three symptoms of MS were observed in this material so often that there is reason to unite them into a clinical entity." In 46 cases there were symptoms of different diseases of the central nervous system explaining mostly the psychical and neurological changes. These symptoms form no clinical entity, but it can be supposed that different central nervous changes can give rise to the endocrine symptoms in question. The hormone excretion was examined in 22 cases, mostly in younger individuals 2 women and 1 man showed very low values, in 4 older women there was increased testis hormone excretion

The principal metabolic disturbance was obesity. Hirsutism was encountered in 12 cases When fat and hypertensive these patients might mistakenly be diagnosed as CS. Hypertension was seen in 16 of the cases. The neuropsychiatric symptoms were the same as in other series.

There is lacking any pathological basis to which one might attribute the disorder, but from a clinical standpoint GROLLMAN and ROUSSEAU "believe, however, that the disease does represent a definite entity, which, when taken in conjunction with the specific X-ray findings, may be differentiated as a distinct disease process." The symptoms would lead one to assume that the basic disorder of the syndrome is in the hypothalamic area of the brain.

OLDBERG discussed in a paper on senile diabetes and craniodysplasia (1944) the questions bearing on MS. He based his considerations on the papers published by BARTELHEIMER, HENSCHEN, MOORE and MORTIMER, and investigated systematically the skull changes in 140 females who developed diabetes in the fourth decade. In 20 (7 per cent.) of these cases a statistically significant dysplasia of the skull was present. The frequency both of dysplasia and hypertension was appreciably greater in these cases.

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SUAREZ (1944) Case report

ALLISSON, BERTHOUD and BRANTMAY (1945) A case of acromegaly combined with Hfi in a woman, [illegible]

HENSCHEN (1945) published [illegible] special consideration to the sen[illegible] the present book.

DI LASCIO (1945). Clinical study of Hfi.

MASCHERONI, REUSSI and ITURBE (1945). A case of MS associated with headaches and variations of lumbar and sacral vertebral articular tropism.

MELLGREN (1945) published a comprehensive paper on "The Anterior [illegible] [ad]renal Cortex," in which he studied [illegible] and menopausal syndromes and of [illegible] particularly intensive study to the [illegible] of MS According to MELLGREN the anterior pituitary lobe shows on the whole the same histological change in [illegible] "Cushingoid habitus" and prostatic [illegible] of the number of hyaline Bc's and [illegible] a less constant relative increase of [illegible] [baso]philes", this being the expression of a corticotropic hyperfunction of the anterior pituitary

pathogenesis was not demonstrable, the association of two diseases was purely coincidental.

LARUE, SAMSON and PATRY (1946). Case of Hfi.

VILA (1946). Cases of Hfi in diabetics.

During the proof-reading two important contributions to the present problems came to the author's notice. Unfortunately it was not possible to pay due regard to these papers in the present account.

PEDERSEN (1947) published a critical survey of the present problems from a clinical point of view, founded on the study of roentgenograms from 908 patients, 485 of whom constituted a normal material. " As a result of

It may be interpreted as a Morgagni syndrome (or parts thereof) in neuropsychiatric patients "

" In a few respects the writer cannot share HENSCHEN's views. This applies primarily
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years; the male cases were 52 and 72 years old In 14 cases there was a
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found only in 8 cases, " but the three symptoms of MS were observed in this material so often that there is reason to unite them into a clinical entity." In 46 cases there were symptoms of different diseases of the central nervous system explaining mostly the psychical and neurological changes These symptoms form no clinical entity, but it can be supposed that different central nervous changes can give rise to the endocrine symptoms in question. The hormone excretion was examined in 22 cases, mostly in younger individuals: 2 women and 1 man showed very low values, in 4 older women there was increased testis hormone excretion

CHAPTER THREE

THE AUTHOR'S MATERIAL

The material examined comprises autopsies of almost identical numbers of both sexes: the same attention was given to the skulls of the men as to those of the women. To this are added 4 cases of women, who were only examined clinically.

A. FEMALES

The material comprises 1,000 cases and is divided into the following six groups:—

I. Older skulls from the Pathological Museum of the Caroline Institute.

II. Cases with Hfi of high degree observed incidentally during post-mortem examinations of brains during the years 1930-35.

III. A continuous series of 200 unselected skulls of women in 1935, all over 30 years of age

IV. Isolated cases of special interest observed after the conclusion of the above series, from the years 1935-36.

V. *Seven hundred autopsies of women over 25 years of age* during the years 1937-41. These cases do not form a continuous series The skulls in these cases were opened chiefly on account of the clinical diagnosis or in certain cases where Hfi was suspected

VI. Four clinical cases without autopsy

The groups having very different composition, a statistical treatment of the whole material cannot be performed Even Groups III and V must be treated separately, at least in part, for the same reason.

Group I—In the *cases from the Museum collections* notes about age and sex are not seldom lacking. *However, when sex had been indicated all typical cases proved to be female.* Fig. 1 shows a typical case of high degree. In some cases the Hfi was associated with a general thickening and sclerosis of the skull. The alterations of the skulls of two women—one 80 years old, the other 82—were of quite enormous degree The overgrown bone projected in both cases as a prodigious bulging mass into the cranial cavity (Figs. 2 and 3)

Group II—*Occasionally observed cases of hyperostosis of high degree* (henceforth indicated by + + +) from the years 1930-35. The cases came with one exception from St Erik's Hospital, where at that time

FIG. 1.—Typical Hfi of very high degree (+ + +) in a woman aged 70, with virilism and obesity Calvaria rather normally thick Four-tenths of original size.

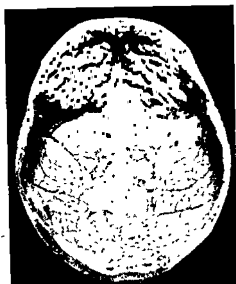
FIG. 2.—Extremely heavy, thick and compact calvaria with exceptionally flat-tuberous Hfi of very high degree (+ + +) in a woman aged 80, with virilism and obesity. Both frontal lobes of the brain were flattened. Four to five-tenths of original size.

FIG. 3—Typical Hfi of very high degree (+ + +) in a woman aged 82, with hirsutism and obesity. The calvaria extremely thick, very heavy and dense. Big frontal sinuses, exceptionally narrow skull cavity Four-tenths of original size.

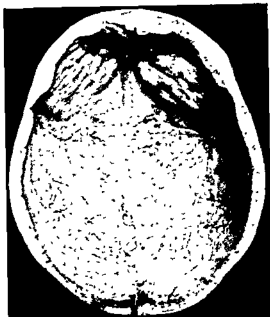
FIG. 4—Calvaria of a woman aged 58, with a pituitary tumour, acromegaly, hirsutism and obesity. Defect of a great part of the right frontal bone after operation. The inner surface of the frontal and parietal bones is starred with small osteophytes (Case 83, p. 37). Four-tenths of original size.

FIG. 5—*Horizontal section from the pituitary* in Case 83 (acromegaly and Ms) The right and anterior parts of the anterior lobe are occupied by a voluminous chromophobe cell adenoma (light) Posteriorly on both sides an acidophil area (dark), to the left a large (*purely or almost purely*) basophil area (half-tint) The author's camera sketch Magnification 4 x.

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[Facing page 36

many autopsies of elderly individuals were performed. The post-mortem material under discussion comprised nearly the same number of men and women, and the skulls of both sexes were opened in nearly equal proportions. In a series of about 3,900 sections, Hfi + + + was observed twenty-eight times, *all women*. This series, therefore, gives no idea of the frequency of the cases with slight or moderate Hfi In many cases a particularly robust body structure with more or less male features was observed, in a few cases the type could even be called acromegaloid. Very often hairiness of the upper lip and the chin existed Among the 28 women there were 10 "very stout" and 9 "stout" individuals. In 2 cases the state of nutrition was "moderate," in 2 "meagre," in 5 no comment is made.

Not few in number were the cases of particularly marked Hfi in which could be observed a considerable symmetrical, faceted flattening of the frontal poles of the brain, due directly to the Hfi

GROUP III—To enable intensive studies of the early and slighter degrees of hyperostotic change, as well as for a preliminary statement of the frequency of it, *a continuous series of 200 skulls of women over 30 years was examined*. In this way nearly all female subjects from the post-mortem room of St Erik's Hospital, during a certain period, were examined During some months the same procedure was followed in the Pathological Department of the Caroline Institute, only those cases being omitted in which for various reasons the skulls could not be opened. This series gives a good idea of the frequency within the different age periods, the structure of the body, the state of nutrition, the hairiness of the face and the rest of the body, the weight of the removed calvaria and, finally, the weight of the brain in negative and positive cases. A collation of the cases of the series follows on page 56 and following

Among the cases of this series 1 case of pituitary tumour and 1 of suprasellar meningoma with Hfi, obesity, male hairiness of the face and acromegaly or male features are worthy of special attention.

CASE 83—A female aged 58, with tumour of the pituitary and acromegaly.

Case History—(I am greatly obliged to Professor H OLIVECRONA for the use of the clinical data)

History—Menstrual periods always normal, ceased at about 53 years of age The actual disease began one or two years before that time The patient became tired and dull and felt a sense of pressure over the vertex. At the same time the hands and feet grew bigger and the skin of the hands grew coarse, "like elephant-hide" Patient began to perspire greatly For four years the patient has observed increase of the size of the tongue and enlargement of the throat In the last two years there has developed difficulty in breathing. At first these symptoms developed very slowly, but in the last one to two years, and especially in the two months preceding admission, the disease has developed rapidly

and drawn apart.

X-ray of the Skull (LYSHOLM)—Large skull, thickened especially anteriorly with newly formed, irregular, hyperostotic layers in the frontal regions. Sella turcica balloon-shaped, measures about 13 × 13 mm.: the base seems to be somewhat obscure.

Operation (OLIVECRONA)—Extract: Intradural exposure of the chiasma on the right side. The cranial bone was especially thick and rather highly vacuolated and had grown together with the dura Great respiratory difficulty because of the enlargement of the tongue. The dura under great tension. Puncture of the ventricle yielded only some cubic centimetres of fluid No lowering of the intradural pressure. The patient becoming unconscious at an early stage of the operation and an intracranial complication being probable, the operation was interrupted. Patient died some hours later.

Section of the Brain (OLIVECRONA)—No particular changes were found.

Autopsy (HENSCHEN)—Length 160 cm., *very robust constitution, marked acromegaly Considerable obesity. Sparse coarse hairs at the upper lip,* almost no axillary hairs. Pubes moderately ample. General moderate arteriosclerosis. Healed endocarditis of the aortic and mitral valves, with stenosis of the mitral ostium. Congestion of lungs, liver and spleen. Cysts of the left kidney. Myomata of the uterus. Ovaria gyrata. Scars from stomach ulcers. Cholesterol stone in the gall-bladder. Adrenals large and dense, very vascular, high lipoid content *Thyroid gland*. marked nodular hyperplasia with hæmorrhages and degeneration, weight 230 g. *Parathyroids:* somewhat enlarged—corresponding to the region of operation, the entire half of the frontal bone is missing. *The roof of the skull* is only detached with difficulty and, especially anteriorly, with the tearing off of shreds of dura. Roof of the skull generally thickened, measures in front 1·5 cm., rather light, remarkably easily sawn Dura not opened at operation The *inner side of the roof of the skull* shows a dense, warty, symmetrically disposed hyperostosis of the tabula interna, which is most marked at the frontal bone and shows strong resemblance to the common Hfi, but not complete conformity with it, being somewhat more finely warty than the majority of the cases (Fig 4). Even behind the groove of the arteria meningea media there are great quantities of more isolated bony warts, which become smaller and more dispersed farther backwards and finally are missing over the occipital bone The brain is big, its surface much flattened The sella rather smallish, the *hypophysis* gives the impression of marked diminution in size In the attempt to remove this, it was found that the organ was prolonged into the base of the skull, so that a part of the base as well as the roof of the pharynx was removed. The sinus sphenoidales asymmetrical—the right side rather big, the left one small. The pituitary cavity continues into the septum between the sinuses and impinges upon the left sinus The weight of the hypophysis is 1 9 g., it has an asymmetrical shape somewhat like a flattened pear

Microscopical examination of the hypophysis on a series of horizontal

the left, anteriorly and downwards, the adenoma stretches itself to the capsule, while behind, the tissue of the adenohypophysis forms a cap-like surface. The lowest parts of the sections consist exclusively of adenomatous tissue. Posteriorly the adenoma contains a small, round, clearly limited hyaline area with a central calcification. Below, there is a cyst, containing detritus, some blood, cholesterol crystals and some foreign-body giant cells. The pituitary tissue proper consists almost exclusively of Bc and Ac. Cc appear only occasionally or in small foci. In the adenoma are likewise found a few isolated Bc and Ac in the middle of the Cc tissue The dominating kind of cells of the anterior lobe are the Bc. Greater quantities of Ac are to be found in the posterior u
mentioned "cap"
half of the adenohy
speaking, the Ac, however, gives place completely to the Bc. The latter form at some places sharply defined dense "adenomas" of the size of the pancreas islets

The part of the base of the skull lying under the hypophysis and the pharyngeal roof were microscopically examined for heterotopic pituitary tissue, but without result

CASE 186—A female, 67 years old. Suprasellar meningoma.

Case History very incomplete. Patient was taken ill rather acutely and died soon after admission to the clinic.

Clinical Diagnosis.—Cerebral condition (subarachnoidal hæmorrhage).

Autopsy (HENSCHEN)—*Robust, stout woman. Length* 172 *cm Strong, somewhat masculine face,* but no clear-cut acromegaly. *Luxuriant hair-*
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generally,
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e and the
edian line
21 mm) (Fig 8).

Autopsy Diagnosis—Purulent gangrenous cholecystitis Hypertension, cerebral hæmorrhage

Microscopical Examination — Minor subependymal hæmorrhages *Adrenals:* Moderate fatty degeneration of the cortex, in other respects normal *Thyroid gland* Rich in colloid Follicles of varying size *Parathyroids* Lipomatous, remarkable mass-formation of large, clear, acidophil
which at the autopsy quite gave the
neoplasm, is a typical meningoma lying
ing intimately joined to the hypophysis,
though it is separated from the tissue of the gland by a thin stratum of the dura The pituitary itself is slightly enlarged, its form slightly altered by the tumour Between the tumour and the adenohypophysis there is

Appearance—Obesity of high degree, frank acromegaly with stout nose, projecting superciliary ridges, thi[illegible] [illegible] [illegible] [illegible] ment of the tongue, which forms [illegible] has made the teeth protrude. D[illegible] especially of the big toes. Skin thick, atonic and doughy, the pores enlarged and drawn apart.

[illegible] with [illegible] ture [illegible] be somewhat obscure.

Operation (OLIVECRONA)—Extract · Intradural exposure of the chiasma on the right side. The cranial bone was especially thick and rather highly vacuolated and had grown together with the dura. Great respiratory difficulty because of the enlargement of the tongue. The dura under great tension. Puncture of the ventricle yielded only some cubic centimetres of fluid. No lowering of the intradural pressure. The patient becoming unconscious at an early stage of the operation and an intracranial complication being probable, the operation was interrupted. Patient died some hours later.

Section of the Brain (OLIVECRONA)—No particular changes were found.

Autopsy (HENSCHEN)—Length 160 cm, *very robust constitution, marked acromegaly. Considerable obesity. Sparse coarse hairs at the upper lip,* almost no axillary hairs. Pubes moderately ample. General moderate arteriosclerosis. Healed endocarditis of the aortic and mitral valves, with stenosis of the mitral ostium Congestion of lungs, liver and spleen. Cysts of the left kidney Myomata of the uterus Ovaria gyrata. Scars from stomach ulcers Cholesterol stone in the gall-bladder Adrenals large and dense, very vascular, high lipoid content. *Thyroid gland* . marked nodular hyperplasia with hæmorrhages and degeneration, weight 230 g. *Parathyroids:* somewhat enlarged—corresponding to the region of operation, the entire half of the frontal bone is missing *The roof of the skull* is only detached with difficulty and, especially anteriorly, with the tearing off of shreds of dura. Roof of the skull generally thickened, measures in front 1·5 cm., rather light, remarkably easily sawn Dura not opened at operation. The *inner side of the roof of the skull* shows a dense, warty, symmetrically disposed hyperostosis of the tabula interna, which is most marked at the frontal bone and [illegible] ity [illegible] uses [illegible] are [illegible] nore [illegible] me. [illegible] the [illegible] attempt [illegible] use of [illegible] x was [illegible] r big, [illegible] tween the sinuses and impinges upon the left sinus. The weight of the hypophysis is 1·9 g.; it has an asymmetrical shape somewhat like a flattened pear.

Microscopical examination of the hypophysis on a series of horizontal sections Setting aside a very slight basophile invasion, the neurohypophysis shows no distinct changes Between the adenohypophysis and neurohypophysis rather numerous large colloid cysts are present. To the left of

FIG. 6.—Calvaria of a woman aged 67, with MS, acromegaloidism and a suprasellar meningoma. Pronounced warty hyperostosis of the frontal and parietal bones; calvaria of ordinary thickness (Case 186, p. 39). Four-tenths of original size.

FIG. 7.—The same case as Fig. 6. Roentgenogram of Dr. C. Sandström.

FIG. 8.—The same case as Figs. 6 and 7. Pituitary gland with a suprasellar meningoma. (a) from the left side, (b) from above. One and a half times natural size.

FIG. 9.—Skull of a woman aged 40, with acromegaly, hirsutism, adiposity and goitre. (a) side face, (b) frontal. Marked Hfi, the sella 13 × 11 mm. Roentgenograms of Dr. C. Sandström (Group VI. Case 1, p. 49).

FIG. 10.—Calvaria of a woman aged 74, robust, length 172 cm., with hirsutism and obesity. Remarkable thickening of the calvaria, with frontal and parietal hyperostosis of very high degree (+ + +) and a corresponding flattening of the brain surface. Roentgenogram four-tenths of original size. *Cf.* Fig. 37.

granulation tissue and a fairly recent hæmorrhage, a small part of the adenohypophysis having been thereby destroyed. The neurohypophysis normal, moderate basophile invasion. The posterior upper part of the adenohypophysis shows a strong acidophilia, only the border areas contain Ac, Bc and Cc. Anteriorly and downwards the picture changes, the Ac being restricted here to the posterior parts, while the larger anterior parts consist nearly exclusively of Bc. The basal parts of the gland consist of a mixture of the three forms of cells, the Ac predominate particularly at the back, while the Bc are greater in number at the anterior part where they form small adenoma-like nests

Group IV—After termination of this series we continued the collection of material, examining specimens of greater interest. Among the cases of Hfi thus found, the following 3 cases merit special interest because they were women under 50 years of age with endocrine disturbances.

CASE 1—Female aged 45. III-para, the last child was born *seven* months ago. For some years difficulty in breathing when going uphill. Fell acutely ill the evening before death with heart trouble.

Autopsy—Big, strong woman, 170 cm. in length, very stout, shaved hairs at the upper lip and on the chin, breasts filled with milk. Hypertrophy of the heart, 430 g., no changes of the valves, arteries normal Œdema of the lung, cholelithiasis, fresh intraventricular and subarachnoidal bleeding without discoverable source. Weight of the calvaria 350 g., extensive but rather flat Hfi, only on the inner side of the frontal bone. Hypophysis macroscopically normal. The interesting part of this case lies in the fact of a woman of 45 years of age with Hfi being pregnant seven months before, so that the Hfi may have developed in connection with the pregnancy

CASE 2—Married woman, 47 years old, nullipara, with organic disease of the heart and repeated emboli of the brain, former weight 96 kg

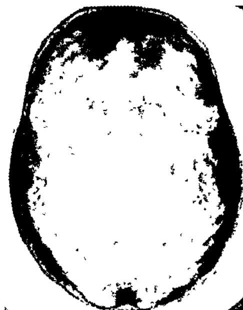
Autopsy—Robust, corpulent, strong male features, large hands and feet, hairiness of the upper lip, otherwise norm[illegible]
of the aorta and mitral valves [illegible]
of various organs *Atrophic ova*[illegible]
Uterus without signs of earlier p[illegible]
the removed calvaria (weight 56[illegible]
standing softening on the left s[illegible]
on the right side Intense (+ + [illegible] *is prolonged on both sides as a less intense, more flattened diadem-like thickening of the tabula interna* Hypophysis macroscopically normal *Radiological examination* of the calvaria shows marked thickening, sclerosis and verrucose hyperostosis

CASE 3—Woman, 49 years old, *never menstruated, epileptical fits* Treatment with radium for cancer of the cervix.

Autopsy—Development and nutritional state moderate No abnormal hairiness. Cancer of the uterus completely cured Atresia of body of the uterus Small cysts in the left ovary Metastatic carcinoma in some organs. *Roof of the skull rather heavy*, 475 g Weight of the brain 1,427 g Hfi +

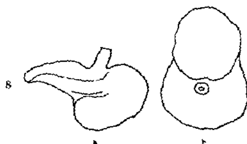
Group V—This group is much more numerous than the preceding ones. It includes 700 autopsy cases, whose skulls were opened mainly for clinical reasons. The clinical data of these patients, which all came





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[*Facing page* 40

from St Erik's Hospital, were supplied in retrospect, at any rate in regard to certain important details. I beg to thank my colleagues for their ready courtesy in this matter.

Special attention is due in this series to the cases of the fourth and fifth decades Among the 72 post-mortem cases of this age period there were no less than 17 positive cases, which are here shortly described :—

Case 1. Woman, 38 years of age, Hfi(+), heavy compact skull, weight of the heart 160 g , died of glioma of the medulla oblongata. Case 2. Woman, 40 years of age, Hfi +, downy moustache on the upper lip, rather fat, Hfp, heart 240 g., dermoid cysts of both ovaries Case 3 Woman, 40 years old, Hfi +, thin skull, heart 320 g., cancer of the uterus, insane (schizophrenia). Case 4. Woman, 41 years of age, Hfi +, moustaches, somewhat stout, heart 270 g., died of leucæmia. Case 5. Woman, 43 years of age, Hfi +, robust, stout, hypertension, weight of the heart 400 g., softening of the brain Case 6. Woman, 43 years of age, Hfi(+), skull otherwise normal, hypertension, heart 580 g. Case 7 Woman, 46 years of age, imbecile, Hfi + +, very emaciated, moustaches, heavy roof of the skull, 540 g , weight of the brain 1,250 g , heart 180 g. Case 8 Woman, 47 years of age, Hfi +, robust, coarse features, moustaches, somewhat stout, osteoporosis, heart 320 g., spinal glioma Case 9 Woman, 48 years of age, Hfi +, very robust, distinct downy growth on upper lip and chin Case 10 Woman, 48 years old, Hfi +, rather stout, moustaches and beard , roof of the skull thick and heavy, 550 g , general osteosclerosis, heart 550 g., valvular disease. Case 11 Woman, 48 years of age, Hfi(+), very stout, 120 kg , hypertension, heart 450 g. Case 12 Woman, 49 years of age, Hfi +, hypertension, heart 530 g , cerebral hæmorrhage. Case 13 Woman, 49 years of age, Hfi + + +, hyperostosis even of the parietal region, ovaria gyrata, heart 345 g , valvular disease Case 14. Woman, 50 years of age, Hfi +, male habitus, extraordinarily robust skeleton, roof of the skull thick, no hirsutism, very stout. Case 15. Woman, 50 years of age, Hfi + +, roof of the skull 410 g., weight of the brain 1,050 g , paralysis, hydrocephalus Case 16 Woman, 50 years of age, Hfi(+), somewhat thin, organic heart disease Case 17. Woman, 50 years of age, Hfi +, moustaches, roof of the skull thick and heavy, hypertension, heart 500 g , brain hæmorrhage

The cases with Hfi + + and Hfi + + + of this series, no less than 76, are arranged in tabular form on pages 42 to 48

	Age	Hfi	Facial Hair-growth	Nutrition	Endocrine Organs and Disturbances (Osteoporosis = o p)	Heart Weight (g) Blood Pressure (mm)	Brain	Clinical Symptoms	Clinical and Pathological Diagnosis
12	63	+ +	Downiness	Enormously fat	No diabetes	400 g 200 mm		For 2 years more severe symptoms (heart and obesity)	Obesity, pulmonary embolism
13	63	+ + +	Downiness	Fat	No diabetes	380 g. 350 mm.	1,300 g., older and very large recent softening	6 months before death apoplexy, 4 days before death hemiplegia	Hypertension, cerebral softening, cardiac insufficiency
14	64	+ +	Slight bearded	Fat		500 g. 250 mm.	Large hæmorrhage	"Always headaches," latterly worse, 14 days before death acute deterioration	Hypertension, pial aneurysms, intracranial hæmorrhage
15	64	+ +	Downiness	Very fat	Diabetes	550 g 300 mm	Old and recent softening	Very fat, 1 month before death apoplexy, psychically normal	Hypertension, arteriosclerosis, pulmonary embolism
16	64	+ + +	Downiness	Rather fat	No diabetes	340 g 230 mm	Severe atherosclerosis, softening	For 1 month fatigue, 14 days ago hemiplegia	Hypertension, T.B. meningitis, pneumonia
17	64	+ + +	Downiness	Fat		495 g 210 mm.	1,150 g., large area of old softening	Insane	Cardio-arteriosclerosis, infarction of the heart
18	65	+ +	Downiness	Fat	Colloid goitre 290, o p	355 g 250 mm	Basal cholesteatoma	Previously in good health, then heart symptoms, angina pectoris	Hypertension, adiposity, pulmonary embolism
19	65	+ + +	Moustaches	Rather fat		380 g. 250 mm		14 days before death gastric symptoms, stenosis œsophagi, slight apoplexy	Cancer of the lung
20	66	+ +		Very fat	Splenomegaly	400 g 150 mm	Normal	For 4 months dyspnœic, no dizziness, headache, fixed pupils, anisocoria	Sero-positive syphilis, cardiac insufficiency
21	66	+ +		Rather abundant	Adrenal lipoidosis	410 g 150 mm	Large softened area, not very recent	For 11 years heart symptoms, apoplexies 3½ months and 10 days before death	Cardiosclerosis with large old infarction, cerebral softening
22	67	+ +	Moustaches and beard	Abundant	o p.	350 g. 255 mm	Severe arteriosclerosis, numerous areas of softening	For 1 year increasing dizziness, 1 week before death severe headache, aphasia	Arteriosclerosis, cerebral softening, pneumonia
23	68	+ + +		*Abundant*	*o p*	250 g 180 mm.	Normal	For 7 months dizziness, no headache, finally agitated, then stuporose	Cancer of the breast with metastases

TABLE 1 (pp. 42 to 48)

76 Cases with Hfi ++ or +++

	Age	Hfi	Facial Hair-growth	Nutrition	Endocrine Organs and Disturbances (Osteoporosis = o p)	Heart Weight (g) Blood Pressure (mm)	Brain	Clinical Symptoms	Clinical and Pathological Diagnosis
1	40	++	Moustaches	Very thin	Suprarenal T B , atrophic ovaries	180 g	1,295 g , macroscopically normal	Idiot	Idiocy, pneumonia
2	49	+++		Fat	Ovaria gyrata, goitre 160 g	345 g heart disease	Large recent softened area	For many years heart symptoms and dizziness, hemiplegia 1½ months before death	Valvular disease of the heart, cerebral softening
3	50	++		Mediocre		280 g	1,050 g , calvaria 410 g.	General paralysis	Dementia paralytica
4	51	+++	Downiness	Rather fat	Atrophic ovaries, slight o p.	465 g 165 mm.	1,210 g , frontal flattening, recent areas of softening	Polyarthritis 12 years before death, heart symptoms, no psychoneurological symptoms	Valvular disease of the heart, cerebral softening, cardiac insufficiency
5	51	++	Downiness	Abundant	Atrophic ovaries, slight o p	275 g	1,350 g , macroscopically normal	Psychopathia, polyarthritis	Chronic polyarthritis, pneumonia
6	60	++	Moustaches	Mediocre	Large hypernephroma with metastases, severe o p	400 g 200 mm.	Several areas of old softening	In good health until 2 years before death, then several apoplexies, hypertension symptoms (headache, dizziness)	Hypertension, hypernephroma, pneumonia
7	60	++	Coarse hairiness	Very obese	Suprarenal adenomas, masculine facies	570 g 160 mm.	?	For 4 years increasing somnolence, worse for 14 days before death	Valvular disease of the heart, hypertension, obesity
8	62	++	Moustaches	Mediocre	Diabetes	280 g.	Moderate atherosclerosis	Insane, diabetes for 7 years	Psychosis, diabetes, cholecystitis
9	62	++		Mediocre	Thyroid 60 g , o p.	275 g	Senile hydrocephalus, no softenings	Ill for 2½ years, abdominal symptoms, bronchitis, emphysema	Cardio-arterio-sclerosis, bronchitis, cardiac insufficiency
10	62	++		Rather fat	Atrophic ovaries	435 g 260 mm	Numerous areas of old softening, large recent hæmorrhage	Fracture of the neck of the femur, sudden unconsciousness	Hypertension, brain hæmorrhage
11	62	++		Very fat	Atrophic ovaries	440 g. heart disease	1,100 g , atrophic frontal lobes	Insane, imbecile	Valvular disease of the heart, psychosis, pneumonia

	Age	Hb	Facial Hair-growth	Nutrition	Endocrine Organs and Disturbances (Osteoporosis = o p.)	Heart Weight (g.) Blood Pressure (mm.)	Brain	Clinical Symptoms	Clinical and Pathological Diagnosis
35	72	+ + +	Downiness	Abundant	Diabetes, slight o p.	415 g. 230 mm.	1,310 g., old and recent softening	Latterly deaf, tinnitus, headache, insomnia, senile melancholia	Cardio-arterio-sclerosis, cerebral softening, cholecystitis
36	73	+ +	Downy upper lip	Rather thin	Diabetes, o p	450 g	Normal	Previously healthy, for 1 year diabetes, agitated, contumacious	Cardio-arterio-sclerosis, hypertension, pneumonia
37	73	+ +	Downy upper lip	Mediocre	Glycosuria	380 g.	Fresh haemorrhage, size of an orange	Breast cancer operation	Cardio-arterio-sclerosis, brain haemorrhage
38	73	+ + +	Downy upper lip	Rather thin	Acute pericarditis, thyroid 52 g., no diabetes	280 g	Frontal lobes very flattened	Previously well, for 3½ months tired, no appetite, thin, pernicious anaemia	Pernicious anaemia, T B of the lymph nodules
39	73	+ +		Abundant	o p, no diabetes	550 g 220 mm	Numerous small areas of old softening	20 years before death T B. of lymph nodes, now heart symptoms, dyspnoea, forgetful	T.B of the lymph nodules, purulent pericarditis
40	73	+ + +	Downy upper lip	Emaciated	Adrenal lipoidosis, no diabetes	270 g	Normal	Insane	Psychosis, pulmonary T.B
41	73	+ +	Downiness	Enormously fat	o p, no diabetes	470 g 200 mm	1,150 g., otherwise normal	Syphilis in youth, 11 years before death uterine cancer, for many years heart symptoms, nervous, insomnia	Hypertension, obesity, cardiac insufficiency
42	74	+ +	Moustaches and beard	Very fat	Severe atrophy of pancreas, diabetes, severe o p	450 g	Severe senile atrophy	Always healthy and active, for 1 week dizziness, gradually unconscious	Obesity, senility, pulmonary embolism
43	74	+ +		Mediocre	Adrenal lipoidosis, severe o p.	290 g.	Large old subdural haemorrhage	Insane	Cancer of the colon, subdural haematoma, pneumonia
44	75	+ + +	Very coarse hairiness	Enormously fat	Adrenal lipoidosis, o p., coarse features	500 g	Slight atherosclerosis, calvaria 600 g.		Multiple myeloma
45	75	+ + +	Coarse moustaches and beard	Rather abundant	Severe o p., no diabetes	370 g 160 mm	1,200 g., older and recent softening	For 1 month increasing heart symptoms, no headache, no dizziness, forgetful	Hypertension, cardio arteriosclerosis, pneumonia
46	75	+ +	Moustaches	Fat	Severe spondylosis	460 g. 180 mm	1,020 g., softening	For 3 months insomnia, psychically normal	Cardiosclerosis, infarction of the heart with rupture

Age	Hfi	Facial Hair-growth	Nutrition	Endocrine Organs and Disturbances (Osteoporosis = o p.)	Heart Weight (g.) Blood Pressure (mm.)	Brain	Clinical Symptoms	Clinical and Pathological Diagnosis
68	+ +	Downiness	Fat	Adrenal adenomas and lipoidosis	520 g heart disease 260 mm.	1,175 g., numerous old and recent areas of softening	Symptom of hypertension, abdominal symptoms	Hypertension, cerebral softening, pulmonary embolism
68	+ + +	.	Mediocre	Severe o p	110 g	1,215 g., moderate atherosclerosis, otherwise normal	Insane	Paralysis agitans
69	+ +	Bearded	Rather abundant	o p	440 g 300 mm	Old areas of softening	9 years before death thrombosis, paresis, aphasia, senile dementia	Hypertension, arteriosclerosis, cerebral softening
69	+ +	Moustaches and beard	Fat	o p.	450 g ?	...	of 27 apoplexy with 2 weeks before death apoplexy	Brain tumour, pulmonary embolism
69	+ +	Moustaches, downy chin	Very fat	Adrenal adenomas and lipoidosis	440 g 165 mm	1,200 g., normal	years dizziness, head- stipation, gall stones, ly normal	Cystopyelonephritis, pulmonary embolism
69	+ +		Very fat	Slight o p	465 g 225 mm.	1,170 g., atherosclerosis, softening	rs tired, weak, slight , dizziness, buzzing in slight deafness	Hypertension, arteriosclerosis, cerebral softening
70	+ + +	Downiness	Fat	Adrenal lipoidosis	380 g. 210 mm	Fairly recent hæmorrhage, size of a walnut	before death slight , 10 days before death , aphasia	Hypertension, arteriosclerosis, brain hæmorrhage
70	+ + +		Rather abundant		575 g 185 mm	Areas of softening	years symptoms of sion, headache, dizzi- r a year hemiparesis,	Cardiosclerosis, infarction of the heart, hypertension
70	+ + +		Abundant		580 g. 250 mm	1,140 g., severe atherosclerosis, recent large area of softening	a symptoms of hyper- palpitation of the adache, senile	Hypertension, cardiosclerosis, rupture of the heart
72	+ + +	Moustaches	Abundant	Goitre 140 g., adrenal lipoidosis, adenomas, no o p.	350 g. 170 mm.	1,250 g., normal	althy, now acute gall- disease, psychically	Abscesses of the liver, cholelithiasis
72	+ + +	Coarse moustaches and beard	Abundant	Thyroid adenoma 85 g., lipoidosis suprarenalis, severe o p.	700 g heart disease	1,150 g., œdematous, two large areas of old softening	unconscious	Valvular disease of the heart, arteriosclerosis

	Age	Hfi	Facial Hair-growth	Nutrition	Endocrine Organs and Disturbances (Osteoporosis = o p)	Heart Weight (g) Blood Pressure (mm)	Brain	Clinical Symptoms	Clinical and Pathological Diagnosis
58	79	+ + +	Coarse moustaches and beard	Rather abundant	Adrenal lipoidosis, features a little coarse	500 g 210 mm	1,150 g, frontal lobes slightly flattened	For some years dyspnœic	Cardiosclerosis, hypertension, severe fibroid heart
59	79	+ +	Moustaches	Rather fat	Adrenal lipoidosis, o p	450 g 230 mm	Fresh hæmorrhage	For 3 years headache, dizziness, weakness, 2 weeks ago hemiparesis	Hypertension, cardio-arteriosclerosis, brain hæmorrhage
60	79	+ + +	Downy upper lip	Mediocre	o p	170 mm	1,000 g, large area of cerebral softening	Demented, heart symptoms, insufficiency	Hypertension, arteriosclerosis, cerebral softening
61	79	+ +	Coarse moustaches, downy chin	Fat		430 g 160 mm	Large old and very large recent areas of cerebral softening	Earlier apoplexy, aphasia, now recent apoplexy, stuporose	Arteriosclerosis, cerebral softening, pneumonia
62	80	+ +	Downy upper lip	Rather abundant	o p.	500 g 275 mm	1,050 g, small old standing hæmorrhages	3 years before death fracture of the spine, for some months very weak	Hypertension, arteriosclerosis, small brain hæmorrhages
63	81	+ +	Moustaches and beard	Rather abundant	o p, no diabetes	190 mm	Normal	For 3 years bronchial asthma, never headache nor dizziness	Arteriosclerosis, bronchiectasia, incarcerated hernia
64	81	+ +	Downiness	Rather abundant	Diabetes	375 g	Very severe atherosclerosis, recent softening	For 4 years heart symptoms, for 3 years diabetes, 3 weeks before death apoplexy	Cardio-arteriosclerosis, cerebral softening, diabetes
65	81	+ +		Very fat	Adrenal cortex adenoma, slight o p	500 g	1,200 g, numerous areas of old and recent softening	Insane	Obesity, atherosclerosis, hypertension
66	81	+ +	Moustaches and beard	Abundant	Slight o p	350 g 145 mm.	1,100 g, senile hydrocephalus, meningoma	...	Cancer of the nasopharynx, gastric ulcer
67	82	+ +	.	Very fat	Diabetes	360 g 170 mm	Normal	6 years before death incipient diabetic gangrene, psychically and neurologically normal	Cardio-arteriosclerosis, diabetes
68	82	+ + +	Moustaches and beard	Fat	No diabetes	400 g.	1,050 g, frontal lobes flattened, old softening	Insane	Senile dementia and marasmus
69	83	+ +	Downiness	Rather fat	No diabetes	550 g 160 mm	1,210 g, numerous areas of old softening	Always healthy, forgetful	Cardio-arteriosclerosis, cerebral softening, cancer of the colon

	Age	Hfi	Facial Hair-growth	Nutrition	Endocrine Organs and Disturbances (Osteoporosis = o p)	Heart Weight (g) Blood Pressure (mm.)	Brain	Clinical Symptoms	Clinical and Pathological Diagnosis
7	76	+ +	Moustaches, downy chin	Fat	Diabetes	500 g. 210 mm	1,000 g, atrophy, old softening	For 16 years diabetes, a few days before death hemiplegia, psychically normal	Diabetes, cardiosclerosis, cerebral softening
8	76	+ + +		Fat	Thyroid 40 g., adrenal lipoidosis, o p, no diabetes	525 g. 170 mm	*Small old and large recent softening*	For many years joint symptoms, for 6 months heart symptoms, 2 weeks before death apoplexy	Cardiosclerosis, infarction of the heart, cerebral softening
19	77	+ + +	Downiness	Very fat		390 g 200 mm	Large, fairly recent softening, severe atherosclerosis	Headache since the climacteric, dizziness, 7 months before death apoplexy, finally severe brain symptoms	Cardio-arteriosclerosis, pneumonia
50	77	+ +	.	Abundant	.	410 g 185 mm	1,100 g, arteriosclerosis	4 years before death apoplexy, headache, finally confused	Inguinal hernia, acute appendicitis, pulmonary embolism
51	77	+ + +	Moustaches, downy chin	Enormously fat		600 g. 260 mm	Frontal lobes flattened, old small hæmorrhages, arteriosclerosis	Symptoms of gastric ulcer, finally big gastric hæmorrhage	Obesity, hypertension, gastric ulcer
52	78	+ +	Downiness	Very fat	Thyroid 65 *g., o p*	475 g. 190 mm	*Large hæmorrhagic softening*	2 years before death transitory facial paralysis, 1 week before death paralysis, aphasia	Hypertension, cerebral softening
53	78	+ + +	Moustaches, downy chin	Mediocre	Adrenal lipoidosis, severe o p.	375 g 180 mm.	Severe arteriosclerosis	Gradually "arteriosclerotic" brain symptoms, loss of memory, etc.	Cardio-arteriosclerosis, pneumonia
54	78	+ +	Moustaches, downy chin	.	Adrenal lipoidosis, slight o p	450 g. heart disease 280 mm.	1,125 g, atrophy, recent softening	For 2 to 3 years increasing amnesia, at times confused, hypertension symptoms, finally hemiplegia	Hypertension, cerebral softening, pneumonia
55	78	+ + +	.	Fat	Glycosuria	420 g. 240 mm.	Normal	*Heart* symptoms, glycosuria, psychically normal	Cardio-arteriosclerosis, infarction of the heart
56	78	+ + +	Coarse moustaches and beard	Fat	Large adrenal cortex adenoma	410 g. 200 mm.	Typical multiple sclerosis	. .	Sclerosis disseminata
57	78	+ +	Downy upper lip	Mediocre	Diabetes	430 g 190 mm.	1,300 g, several areas of old and recent softening	Symptoms of diabetes and heart disease, finally aphasia	Arteriosclerosis, diabetes, pneumonia

	Age	Hfi	Facial Hair-growth	Nutrition	Endocrine Organs and Disturbances (Osteoporosis = o p)	Heart Weight (g) Blood Pressure (mm.)	Brain	Clinical Symptoms	Clinical and Pathological Diagnosis
58	79	+ + +	Coarse moustaches and beard	Rather abundant	Adrenal lipoidosis, features a little coarse	500 g 210 mm.	1,150 g, frontal lobes slightly flattened	For some years dyspnœic	Cardiosclerosis, hypertension, severe fibroid heart
59	79	+ +	Moustaches	Rather fat	Adrenal lipoidosis, o p	450 g 230 mm.	Fresh hæmorrhage	For 3 years headache, dizziness, weakness, 2 weeks ago hemiparesis	Hypertension, cardio-arteriosclerosis, brain hæmorrhage
60	79	+ + +	Downy upper lip	Mediocre	o p	.. 170 mm	1,000 g, large area of cerebral softening	Demented, heart symptoms, insufficiency	Hypertension, arteriosclerosis, cerebral softening
61	79	+ +	Coarse moustaches, downy chin	Fat	..	430 g 160 mm.	Large old and very large recent areas of cerebral softening	Earlier apoplexy, aphasia, now recent apoplexy, stuporose	Arteriosclerosis, cerebral softening, pneumonia
62	80	+ +	Downy upper lip	Rather abundant	o p	500 g 275 mm	1,050 g, small old standing hæmorrhages	3 years before death fracture of the spine, for some months very weak	Hypertension, arteriosclerosis, small brain hæmorrhages
63	81	+ +	Moustaches and beard	Rather abundant	o p, no diabetes	190 mm	Normal	For 3 years bronchial asthma, never headache nor dizziness	Arteriosclerosis, bronchiectasia, incarcerated hernia
64	81	+ +	Downiness	Rather abundant	Diabetes	375 g	Very severe atherosclerosis, recent softening	For 4 years heart symptoms, for 3 years diabetes, 3 weeks before death apoplexy	Cardio-arteriosclerosis, cerebral softening, diabetes
65	81	+ +		Very fat	Adrenal cortex adenoma, slight o p.	500 g	1,200 g, numerous areas of old and recent softening	Insane	Obesity, atherosclerosis, hypertension
66	81	+ +	Moustaches and beard	Abundant	Slight o p	350 g 145 mm.	1,100 g, senile hydrocephalus, meningoma	...	Cancer of the nasopharynx, gastric ulcer
67	82	+ +		Very fat	Diabetes	360 g 170 mm.	Normal	6 years before death incipient diabetic gangrene, psychically and neurologically normal	Cardio-arteriosclerosis, diabetes
68	82	+ + +	Moustaches and beard	Fat	No diabetes	400 g	1,050 g, frontal lobes flattened, old softening	Insane	Senile dementia and marasmus
69	83	+ +	Downiness	Rather fat	No diabetes	550 g 160 mm	1,210 g, numerous areas of old softening	Always healthy, forgetful	Cardio-arteriosclerosis, cerebral softening, cancer of the colon

	Age	Hfi	Facial Hair-growth	Nutrition	Endocrine Organs and Disturbances (Osteoporosis = o p)	Heart Weight (g.) Blood Pressure (mm)	Brain	Clinical Symptoms	Clinical and Pathological Diagnosis
47	76	+ +	Moustaches, downy chin	Fat	Diabetes	500 g 210 mm	1,000 g, atrophy, old softening	For 16 years diabetes, a few days before death hemiplegia, psychically normal	Diabetes, cardiosclerosis, cerebral softening
48	76	+ + +		Fat	Thyroid 40 g., adrenal lipoidosis, o p., no diabetes	525 g 170 mm.	Small old and large recent softening	For many years joint symptoms, for 6 months heart symptoms, 2 weeks before death apoplexy	Cardiosclerosis, infarction of the heart, cerebral softening
49	77	+ + +	Downiness	Very fat		390 g 200 mm	Large, fairly recent softening, severe athero sclerosis	Headache since the climacteric, dizziness, 7 months before death apoplexy, finally severe brain symptoms	Cardio-arteriosclerosis, pneumonia
50	77	+ +	.	Abundant	.	410 g 185 mm	1,100 g, arteriosclerosis	4 years before death apoplexy, headache, finally confused	Inguinal hernia, acute appendicitis, pulmonary embolism
51	77	+ + +	Moustaches, downy chin	Enormously fat		600 g. 260 mm	Frontal lobes flattened, old small hæmorrhages, arteriosclerosis	Symptoms of gastric ulcer, finally big gastric hæmorrhage	Obesity, hypertension, gastric ulcer
52	78	+ +	Downiness	Very fat	Thyroid 65 g, o p	475 g 190 mm	Large hæmorrhagic softening	2 years before death transitory facial paralysis, 1 week before death paralysis, aphasia	Hypertension, cerebral softening
53	78	+ + +	Moustaches, downy chin	Mediocre	Adrenal lipoidosis, severe o p.	375 g 180 mm.	Severe arteriosclerosis	Gradually "arteriosclerotic" brain symptoms, loss of memory, etc.	Cardio-arteriosclerosis, pneumonia
54	78	+ +	Moustaches, downy chin		Adrenal lipoidosis, slight o p.	450 g. heart disease 280 mm	1,125 g, atrophy, recent softening	For 2 to 3 years increasing amnesia, at times confused, hypertension symptoms, finally hemiplegia	Hypertension, cerebral softening, pneumonia
55	78	+ + +	.	Fat	Glycosuria	420 g. 240 mm.	Normal	Heart symptoms, glycosuria, psychically normal	Cardio-arteriosclerosis, infarction of the heart
56	78	+ + +	Coarse moustaches and beard	Fat	Large adrenal cortex adenoma	410 g 200 mm.	Typical multiple sclerosis	...	Sclerosis disseminata
57	78	+ +	Downy upper lip	Mediocre	Diabetes	430 g 190 mm.	1,300 g, several areas of old and recent softening	Symptoms of diabetes and heart disease, finally aphasia	Arteriosclerosis, diabetes, pneumonia

Group VI—*Clinical cases without autopsy.*

CASE 1—(For the clinical data of this case I have to thank Professor BERGLUND and Chief Physician Dr SANDSTRÖM, St Erik's Hospital, and Professor NANNA SVARTZ, Caroline Hospital, Stockholm)

Clinical (BERGLUND)—Woman, 40 years of age, married for nineteen years, has two children, 17 and 15 years of age. Periods became irregular some years ago; after curettage, normal again. For many years *progressive increasing acromegaly*, but for long without enlargement of the jaw or curvature of the spine. Luxuriant hair-growth on the face, downy beard
cut, otherwise no hirsutism.
heavy-headed; has dull pains
at night, which disturb sleep
hunger for carbohydrates; eats
dry rice, grains of corn and sugar; has in the last few months put on 6 to 7 kg.

X-ray Examination (SANDSTRÖM).—*Enlargement of the sella turcica*, 13 × 11 mm., and *typical Hfi* (Fig 9); no changes in the skeleton of the hand.

to adopt a depressive, somewhat paranoid view of life. Probably her acro-

Clinical Diagnosis—Acromegaly, Hfi, virilism, constipation, neurosis.

The following three cases I owe to Professor NANNA SVARTZ, Medical Clinic of the Caroline Hospital, Stockholm .—

CASE 2—Woman, 48 years of age. Formerly healthy, four children; menopause seven years ago. For some years difficulty in breathing during extreme effort. For four years, headaches mostly over the left eye, later on also in the neck.

Appearance—Rather fat, 158 cm , 78 kg Blood pressure 150/90. Basal metabolism − 15 per cent *X-ray of the skull ;* Sella turcica normal. Moderate Hfi Takes caffein, gynergen and thyroid

Clinical Diagnosis—Hypothyroidism, Morgagni's hyperostosis.

CASE 3—Woman, 55 years of age Father and mother died when over 80 years old Patient has two children Menopause at 49 years Since her early years, very stout;
she suffered from arthrosis de
in the head and some dizziness

Appearance—Very stout, 98 kg., light male hairiness on the face. Blood pressure 210/130, three days later 230/110, three weeks later 170/115

4

	Age	Hh	Facial Hair-growth	Nutrition	Endocrine Organs and Disturbances (Osteoporosis=o p)	Heart Weight (g.) Blood Pressure (mm.)	Brain	Clinical Symptoms	Clinical and Pathological Diagnosis
70	84	+ +	Coarse hairiness	Thin	Slight o p	250 g	1,200 g, old subdural hæmatoma	Insane	Cancer of the lung
71	84	+ +		Fat	o p, no diabetes	460 g 200 mm	1,140 g, cerebral softening	Always very healthy, 3 weeks before death apoplexy	Cardio-arterio-sclerosis, cerebral softening
72	85	+ + +	Downy upper lip	Rather thin	Severe o p, no diabetes	380 g 260 mm	1,100 g, several areas of old softening	For some years weakness, dizziness, sometimes fell down	Hypertension, pulmonary embolism
73	85	+ + +	Moustaches and beard	Abundant	Adrenal lipoidosis	395 g. 220 mm.	1,100 g., frontal lobes flattened, old and recent softening	1½ weeks before death apoplexy, aphasia	Hypertension, brain softening
74	86	+ +	Coarse hairiness, eyebrows	Rather thin	Adrenal lipoidosis, severe o p	375 g 230 mm	Thrombosis and large area of softening	Always healthy, 2 days before death apoplexy	Cardio-arterio-sclerosis, brain softening, pneumonia
75	87	+ +	Downiness	Mediocre	No diabetes	315 g.	Brain tumour, big as a mandarin	7 months before death apoplectiform attack, previously healthy	Brain tumour
76	87	+ +	Beard	Mediocre	No diabetes	370 g.	1,050 g, senile hydrocephalus	Insane	Psychosis, pneumonia

unconsciousness, blood pressure 250 Operation was performed on suspicion of an extradural hæmatoma in the Neurosurgical Clinic (Professor OLIVECRONA). Operation revealed no lesion, patient died an hour later.

Clinical Diagnosis—Hypertonia, diabetes mellitus, commotio cerebri, suspected basal brain aneurysm.

Post-mortem Diagnosis—Enlarged dilated heart Cardio-arteriosclerosis, cerebral hæmorrhage, lipomatosis pancreatis, adiposity.

Autopsy (Professor REUTERWALL)—Length 169 cm., pyknic, marked adiposity.
operation w
Weight of t]
and the aorta. Testes rather small, otherwise normal. they weigh together 20 g Pancreas rather small, moderately lipomatous, weight 60 g. The roof of the skull unusually heavy, 725 g. The surface of the brain flattened. In the anterior part of the right internal capsule a fresh hæmorrhage well over the size of an orange. Pituitary macroscopically normal.

The roof of the skull is large, unusually compact, not especially thick, almost without diploe, asymmetrical, the left part somewhat bigger than the right. In the horizontal plane of section it measures on the average 5 mm, at the most 8 mm. In the middle line of the frontal bone the skull is thin and transparent, in the central parts of the frontal and the parietal bones it measures 10 to 11 mm. The sulci of the arteries at the inner side are everywhere unusually deep The entire inner surface is slightly knobby, the change becoming much more pronounced over the frontal bones so that it resembles Hfi except that in this case the colour is not whiter than the normal bone—as Hfi usually is (Figs. 11 and 34)

Microscopical Examination of the Testicles—Moderate diffuse atrophy and sclerosis of the tubules and distinct increase of the interstitial cells.

Summary—The skull is not quite typical, so that at first the case was otherwise interpreted, but on renewed examination we now believe that the change represents an atypical Hfi in an unusually hyperostotic skull. Perhaps it is this general thickening and sclerosis of the skull which has modified the Hfi in such a way as to make interpretation difficult Notes on hirsutism are lacking but, on the other hand, a marked adiposity is recorded *The testicles showed moderate atrophy and sclerosis of the tubules with increase of the interstitial cells* Pronounced hypertension and hypertrophy of the heart were also present, while corresponding to the diabetes there was an atrophy and lipomatosis of the pancreas The cause of death was cerebral hæmorrhage.

CASE 2—Man, 56 years old Jew St Erik's Hospital, 1941. Admitted moribund Is said always to have been stout For a year ill and tired Blood examination t[illegible]
red corpuscles 2,640,[illegible]
of the coronary arterie
became unconscious a
130/80, blood sugar 0 120 per cent, no acetone or ketone bodies Death after two days

Clinical Diagnosis—Cirrhosis of liver, adiposity

Blood cholesterol 216 mg. per cent. *X-ray of the skull;* Sella turcica normal, slight Hfi.

10 8. Glucose tolerance test At 9 o'clock 100 g. glucose given.

Time	Blood Sugar	Urine Quantity	Urine Sugar
8.35	. *110* mg. per cent.	*230* g	negative
9.14	. 181 ,, ,,	5 ,,	,,
9.45	. 181 ,, ,,	25 ,,	,,
10.15	. 171 ,, ,,	45 ,,	,,
10 45	. 147 ,, ,,	40 ,,	,,
11 45	. 121 ,, ,,	30 ,,	,,
12 45	. 89 ,, ,,	50 ,,	,,

11 8 Adrenalin administration. At 10 o'clock 0 001 adrenalin.

Time	Blood Sugar	Blood Pressure
9 45 . .	105 mg. per cent.	175/120
10.15 . .	117 ,, ,,	170/110
10.30 . .	138 ,, ,,	155/80
10.45 . .	115 ,, ,,	140/80
11 . .	140 ,, ,,	160/90
11 30 . .	136 ,, ,,	150/90
12.15 . .	151 ,, ,,	160/90

15.8. Blood pressure, 190/120.

Clinical Diagnosis—Arthrosis deformans, Morgagni's syndrome.

CASE 4—Woman, 60 years of age Father very fat, died aged 39 years; mother obese, died aged 63 of brain hæmorrhage. She has three sisters who are not fat A brother is epileptic. Divorced after a short marriage; no children Menopause at 40, obese after this Gradual loss of hair and polyuria For many years headaches in the frontal region and vertex; no dizziness but singing in the ears. Cyclothymiac

Appearance—Stout and virile Hair-growth of head, axillæ and pubes poor; moustaches. X-ray shows rather pronounced Hfi Blood pressure *185/100, later on 155/102 Blood sugar 260 to 450 mg. per cent.*, urine sugar 2 7 per cent., blood cholesterol 277 mg per cent, blood calcium 9 8 to 10·1 mg per cent, basal metabolism +7 per cent

Clinical Diagnosis—Diabetes of senile type, Morgagni's syndrome.

B. MALES

Our material to illustrate Hfi in men comprises 9 autopsy cases, including 1 old case from the Pathological Museum, 1 from the Pathological Institute of Upsala and 2 from the Pathological Department of the Seraphimer Hospital and one from the Southern Hospital in Stockholm The other 4 cases are the only ones which we observed while engaged on the examination of Hfi in women The cases are arranged in order of the age of patients.

CASE 1 (Case B, 1937)—Man, 53 years of age Teacher. For many years diabetes and hypertension. Blood pressure once 300 Latterly healthy and able to work. Early on the day of his death, fit of apoplexy, progressive

unconsciousness, blood pressure 250 Operation was performed on suspicion of an extradural hæmatoma in the Neurosurgical Clinic (Professor OLIVECRONA). Operation revealed no lesion, patient died an hour later.

Clinical Diagnosis—Hypertonia, diabetes mellitus, commotio cerebri, suspected basal brain aneurysm

Post-mortem Diagnosis—Enlarged dilated heart. Cardio-arteriosclerosis, cerebral hæmorrhage, lipomatosis pancreatis, adiposity.

Autopsy (Professor REUTERWALL)—Length 169 cm, pyknic, marked adiposity. In the temporal region on both sides a 5 cm long freshly sutured operation wound, over a round, 1 cm. wide trephine opening of the skull. Weight of the heart 620 g Moderate arteriosclerosis of the coronary arteries and the aorta. Testes rather small, otherwise normal they weigh together 20 g Pancreas rather small, moderately lipomatous, weight 60 g The roof of the skull unusually heavy, 725 g. The surface of the brain flattened. In the anterior part of the right internal capsule a fresh hæmorrhage well over the size of an orange. Pituitary macroscopically normal.

The roof of the skull is large, unusually compact, not especially thick, almost without diploe, asymmetrical, the left part somewhat bigger than the right. In the horizontal plane of section it measures on the average 6 mm, at the most 8 mm. In the middle line of the frontal bone the skull is thin and transparent, in the central parts of the frontal and the parietal bones it *measures 10 to 11 mm* *The sulci of the arteries at the inner side are every*where unusually deep The entire inner surface is slightly knobby, the change becoming much more pronounced over the frontal bones so that it resembles Hfi except that in this case the colour is not whiter than the normal bone—as Hfi usually is (Figs 11 and 34)

Microscopical Examination of the Testicles—Moderate diffuse atrophy and sclerosis of the tubules and distinct increase of the interstitial cells

Summary—The skull is not quite typical, so that at first the case was otherwise interpreted, but on renewed examination we now believe that the change represents an atypical Hfi in an unusually hyperostotic skull Perhaps it is this general thickening and sclerosis of the skull which has modified the Hfi in such a way as to make interpretation difficult Notes on hirsutism are lacking but, on the other hand, a marked adiposity is recorded *The testicles showed moderate atrophy and sclerosis of the tubules with increase of the interstitial cells* Pronounced hypertension and hypertrophy of the heart were also present, while corresponding to the diabetes there was an atrophy and lipomatosis of the pancreas The cause of death was cerebral hæmorrhage.

CASE 2—Man, 56 years old Jew St Erik's Hospital, 1941 Admitted moribund Is said always to have been stout For a year ill and tired. Blood examination two months before death Hæmoglobin 45 per cent, red corpuscles 2,640 000, white 5,800 Electrocardiograph Insufficiency of the coronary arteries For some days aggravation of symptoms Gradually became unconscious and then moribund, enormously stout, blood pressure *130/80, blood sugar 0 120* per cent, no acetone or ketone bodies. Death after two days

Clinical Diagnosis—Cirrhosis of liver, adiposity

FIG. 11.—Calvaria of a man aged 53, with atrophy and sclerosis of the testes, obesity, diabetes and hypertension. Extremely big and heavy calvaria, with a peculiar thickening of the tabula interna, very similar to Hfi (Case 1, p 50). Four-tenths of original size. *Cf.* Fig. 34.

FIG. 14.—Calvaria of a man aged 65, without distinct testicular alterations. Abnormal hair-growth, obesity in spite of *cancer* of the stomach. A typical Hfi (+), the internal surface of the very dense *frontal* bone was flat-tuberous and very white (Case 6, p. 54). Four-tenths of original size

FIG. 12.—Calvaria of a man aged 56, with a big pituitary cyst, atrophy and sclerosis of the testes, abnormal hairiness, obesity, liver cirrhosis and hypertension. Peculiar dense warty hyperostosis of the frontal and parietal bones and deep vascular furrows (Case 2, p 51). Five-tenths of original size. *Cf.* Fig. 35

FIG. 13.—Calvaria of a man aged 62, with eunuchoidism, obesity and hypertension. Not very pronounced warty Hfi (+) (Case 3, p 52). *Four-tenths* of original size.

FIG. 15.—Calvaria of a man aged 68, with Hfi + + and slight adiposity (cancer of sigmoid with metastases); no testicular changes (Case 7, p. 54). Five-tenths of original size

Autopsy—Pyknic appearance. Length 170 cm., enormously stout, weight of the body 145 kg. Deposits of fat mainly on abdomen and hips, which are very fat Hands and feet proportionate. Penis much diminished, only 6 cm. in length Ha
hair on the face, axillary h
in type, scarcely any hair
515 g., no changes in the va
arteries, moderate arteriosclerosis of the aorta. Lungs congested, œdematous Ascites 2 litres. Weight of the spleen 465 g., chronic hyperplasia. The adrenals contain no lipoids. Kidneys 470 g. Testes together weigh 25 g, small, brown, tough. Prostate and seminal vesicles normal, thyroid gland 20 g Œsophageal varices, lipomatosis of the pancreas Liver: Weight
ith lobules of very varying size.
440 g, Hfi + + +, even on the
left side a solitary exostosis of the size of a pea (Figs. 12 and 35). Bone system otherwise normal. Weight of the brain 1,460 g Sella turcica about 2 × 2 cm. Displacing the pituitary there is a cyst, well over the size of a hazel-nut.

Autopsy Diagnosis—Cirrhosis of liver, adiposity.

Microscopical Examination of Testicles · Marked atrophy and fibrosis *Pituitary*. Large central cyst lined by cubical epithelium, surrounded by a very thin layer of pituitary tissue. Liver and pancreas cirrhotic, lipomatous and showing post-mortem change.

Summary—Interesting case with Hfi of high degree, abnormalities of hair-growth, enormous adiposity of a somewhat feminine type and a very small penis *The testes were intensely atrophic and sclerotic*; the pituitary was transformed into a big cyst, only very little parenchyma being seen. It may be presumed that a hypertension had existed earlier, to judge from the marked hypertrophy of the heart. Beside the hypertension and obesity, the main lesion was the hypertrophic cirrhosis of the liver, revealed at autopsy.

CASE 3 (Case C, 1937)—Man, 62 years of age Academical Hospital, Upsala.

Clinical Diagnosis—Hypertonia, left-sided hemiplegia.

Post-mortem Diagnosis (Professor FÅHRAEUS)—Recent cerebral softening of the left parietal lobe and old-standing softening of the internal capsule and pons on the right side + cerebral arteriosclerosis + Hfi (Morgagni's syndrome) + enlarged dilated heart + severe arteriosclerosis with cardiac sclerosis and degeneration + confluent bilateral bronchopneumonia + acute splenitis + arteriosclerotic nephritis + generalized congestion of the organs

Autopsy—Elderly man with the features of an old woman, very stout, especially at the hips and about the breasts Extremities slender Scanty
with diagonal upper
æ albicantes at the
e urethra placed on
the lower surface, nearly ½ cm away from the tip. Scrotum and testicles normal.

FIG. 11.—Calvaria of a man aged 53, with atrophy and sclerosis of the testes, obesity, diabetes and hypertension. Extremely big and heavy calvaria, with a peculiar thickening of the tabula interna, very similar to Hfi (Case 1, p. 50). Four tenths of original size. *Cf.* Fig. 34.

FIG. 14.—Calvaria of a man aged 65, without distinct testicular alterations. *Abnormal* hair-growth, obesity in spite of cancer of the stomach. A typical Hfi (+), the internal surface of the very dense frontal bone was flat-tuberous and very white (Case 6, p. 54). Four-tenths of original size.

FIG. 12.—Calvaria of a man aged 56, with a big pituitary cyst, atrophy and sclerosis of the testes, abnormal hairiness, obesity, liver cirrhosis and hypertension. Peculiar dense warty hyperostosis of the frontal and parietal bones and deep vascular furrows (Case 2, p. 51). Five-tenths of original size. *Cf.* Fig. 35

FIG. 13.—Calvaria of a man aged 62, with eunuchoidism, obesity and hypertension. Not very pronounced warty Hfi (+) (Case 3, p. 52). Four-tenths of original size.

FIG. 15.—Calvaria of a man aged 68, with Hfi + + and slight adiposity (cancer of sigmoid with metastases); no testicular changes (Case 7, p. 54). Five-tenths of original size.

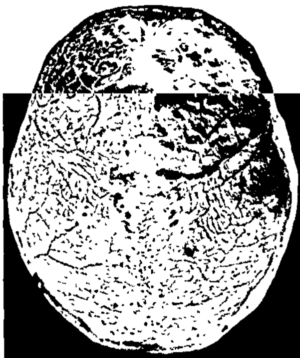
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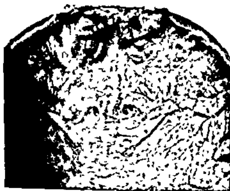
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12



13



15



[*Facing page* 52

atrophy, but are otherwise normal.

The *pituitary* macroscopically normal; testes normal appearance. The prostate smaller than usual, of firm elastic consistency.

Microscopical Examination—In the middle of the neurohypophysis there is a circular, rather sharply limited region with sparse nuclei Slight basophile invasion. Between both lobes some colloid cysts occur. In the adenohypophysis the Cc do not appear to be increased in number and the Ac and Bc predominate almost everywhere The former constitute here and there nearly pure adenomas, which from their size almost fill a microscopic field. Mostly they are intimately mixed with the Bc. Even the Bc form at some places nearly pure cellular aggregations

Summary—Typical case of MS with a Hfi of slight degree, abnormalities of hair-growth, very marked adiposity of female type and very small penis. Microscopical examination of the testicles is lacking; the prostate was atrophic The clinical diagnosis of hypertension was substantiated by the hypertrophy of the heart at autopsy The cause of death was cerebral softening and pneumonia

CASE 4 (Case D, 1937)—Man, 62 years of age. St Erik's Hospital, 1937. Big, robust man; is said to have always had a coarse, acromegaloid face.

Clinical Diagnosis—Carcinoma of stomach

Autopsy—Robust, length 181 cm, somewhat stout, acromegaloid, big coarse features,
big. Slight arter
of the kidneys 40
the size of a plur
Thyroid 45 g, s
of stomach. The spinal column slightly osteoporotic, no metastases. *The roof of the skull* diffusedly thickened, weight 550 g. *On the inner surface of both frontal bones a whitish hyperostosis, nearly 2 mm thick, of the size of a penny-piece* Weight of the brain 1,650 g Pituitary slightly enlarged

Post-mortem Diagnosis—Acromegaloidism, carcinoma of stomach, hepatic abscess, peritonitis

Microscopical Examination—Kidneys Typical hypernephroma. Liver: Fine cirrhosis, abscess Testes Atrophy and sclerosis of varying degree. *Pituitary* on serial sections Neurohypophysis slight basophile invasion, otherwise normal Distinct reticular sclerosis of the adenohypophysis, so that the cells seem to lie in small alveoli of about equal size Above and posteriorly is a pronounced, firm protuberance consisting of Ac which seem here to form symmetrical, adenomatous masses More anteriorly and below, the alveolar arrangement predominates. Cell type here is a large or medium-sized, intensely coloured cell, rich in protoplasm, either markedly eosinophilic or more often neutral or slightly basophilic Many of these large, non-eosinophilic cells contain a brighter centre or are vacuolated The Cc are found anteriorly and below and occupy a minor place in the picture

Summary—A big, robust and, in spite of emaciation, somewhat stout man with acromegaloidism and Hfi *Atrophy and sclerosis of*

the testes. Hepatic cirrhosis. Hypertrophy of the heart, without alterations of the valves. Carcinoma of the stomach. The pituitary shows peculiar reticular sclerosis and a firm protuberant growth composed of acidophile cells.

CASE 5 (Case A, 1937)—Man, 65 years old, died 1901. Skull from the Pathological Museum of the Caroline Institute.

Clinical Diagnosis—Cardiac sclerosis, bronchitis, cirrhosis of liver, acute myelitis, bed-sore.

Post-mortem Diagnosis (Professor SUNDBERG)—Cardiac hypertrophy, right-sided bronchopneumonia, cirrhosis and cancer of liver, softening of the spinal cord.

Autopsy—Medium size, rather robust, not very fat Icterus, cutaneous œdema, sacral bed-sore. Moderate heart hypertrophy, recent bronchopneumonia. Ascites 500 g. Atrophic liver cirrhosis with numerous grey-coloured tumours, from miliary to hazel-nut size Metastases in the sternum, ribs and vertebræ, with compression of the spinal medulla. The roof of the skull heavy, somewhat thicker than normal, diploe reduced, lamina interna thickened, deep vascular furrows. The dura fused with the frontal bone. The inner surface shows on both sides *an accumulation of osteophytes with a radial disposition.* In addition the roof of the skull is invaded by several metastases varying from the size of a pea up to the size of a hazel-nut.

Re-examination of the Roof of the Skull, 1935—The bone formations on the tabula interna show a clear resemblance to Hfi of slighter degree.

Summary—Case of Hfi in a man. It is not known if abnormalities of hair-growth existed, the state of nutrition seems to have been rather bad, which may be connected with the severe changes in the liver In the same way it is not known if changes were present in the testes, but we should like to emphasize here that many of the hepatic cirrhoses among our autopsies have been combined with testicular changes. The hypertrophy of the heart substantiates in some degree a diagnosis of hypertension during life

CASE 6—Man, 65 years of age. St Erik's Hospital Was operated on for cancer of stomach, but died during the operation.

Autopsy—Length 175 cm, rather robust, thin, hair-growth normal. Weight of the heart 400 g. Acute emphysema of the lungs, associated with *aspiration of stomach contents and a foreign body into the larynx.* Testes [illegible]

backed, whitish, the bone here being more compact than normal (Fig. 14)

Microscopical Examination—Testes show no great abnormality.

CASE 7—Man, 68 years of age. Medical clinic of the Seraphim Hospital, Stockholm, 1944. Has been admitted moribund. Previously good health, for some months gradually more tired and emaciated. Is said to suffer from arteriosclerosis and heart disease Diagnosis uncertain. Blood pressure 145/75, blood sugar 200 mg. per cent. Died after three days

Autopsy—Length of the body 179 cm, somewhat fat Weight of the heart 430 g. Slight sclerosis of the coronary arteries, rather marked sclerosis

of the aorta carcinoma.
A great numb vertebræ.
Moderate lipo Pituitary
macroscopically normal No change in the brain Hfi + + (Fig. 15).

Microscopical Examination—Testes not abnormal.

Summary—Case of marked Hfi in a big man; fat in spite of emaciation. No manifest alterations of the testes. The hypertrophy of the heart suggests a diagnosis of hypertension, which could not be confirmed because patient was admitted moribund to hospital. The main disease was a cancer of the sigmoid and rectum with metastases.

CASE 8—Man, 73 years old. St Erik's Hospital, 1939. Formerly always enjoyed good health

Appearance—Bad general condition. Signs of arteriosclerotic brain softening Ascites (peritonitis ?), epididymitis, sepsis Death after about five weeks

Autop
what thr
Chronic
abscess.
(*together* 13 *g.*), *microscopically considerable atrophy and fibrosis.* Osteoporosis, spondylosis deformans, Hfi +, calcification of the falx cerebri. No macroscopical changes in the brain.

Summary—Old man with Hfi Hair-growth and nutritional state normal *Considerable atrophy and sclerosis of the testes.* The autopsy showed serious changes in lungs, liver and gall-bladder

CASE 9—Man, 75 years old The Southern Hospital, 1947. Complained for many years of heart trouble

Autopsy (Dr Å. LINDGREN)—Medium length, normal development, in good condition, œdematous legs Weight of the heart, 754 g Healed rheumatic endocarditis with mitral stenosis, rheumatic scars in the myocardium. General arteriosclerosis, old encephalomalacia Extreme spondylosis deformans, no osteoporosis Pituitary and testes macroscopically normal Hfi + + +. Microscopically the testes showed atrophy of the epithelium of high degree, sclerosis and lipomatosis.

Summary—Case of very marked Hfi in an old man of medium size and in good nutritional state. The autopsy showed severe heart disease, general arteriosclerosis, encephalomalacia and marked atrophy of the testes.

CHAPTER FOUR

SURVEY OF THE AUTHOR'S OWN CASES

A. FEMALES

As already stated, the author personally studied 1,000 autopsy cases of females between the ages of 11 and 95. Apart from 4 cases which did not go to autopsy, set out in a separate group, the material is divided into five groups. Since the groups of autopsy cases are in some respects heterogeneous they are not always comparable, particularly for statistical purposes. The group or groups to which the mathematical analysis refers are, therefore, specially indicated.

The 1,000 autopsy cases are distributed in the different groups as follows :—

TABLE 2

	Age															Total
	25	30	35	40	45	50	55	60	65	70	75	80	85	90	95	
Group II— Solely Hfi + + + cases		..					1	2	0	6	5	7	6	1	0	28
Group III— Series of 200 post-mortem cases	.		7	6	4	15	12	22	15	31	42	27	12	6	1	200
Group IV— Selected cases			4	1	2	5	3	4	9	10	19	7	8	0	0	72
Group V— Series of 700 post mortem cases	12	11	14	10	23	39	51	59	83	97	119	111	53	15	3	700
Total	12	11	25	17	29	59	67	87	107	144	185	152	79	22	4	1000

1. Frequency and Age Distribution of Hfi—Table 2 and Diagrams 1 to 4 show the different groups of autopsy cases and their distribution over the different five-year periods The incidence during the first four five-year periods was comparatively low—all in all 65 cases occurred This applies also to the last two five-year periods, comprising the peak ages, in which only twenty-six instances were observed. In the intermediate period, however, the incidence was fairly high

Table 2 and Diagrams 1 to 4 show that Hfi is extremely common in elderly women, especially if cases of early and mild Hfi are taken into consideration.

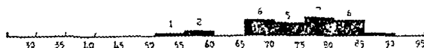


DIAGRAM 1—GROUP II



DIAGRAM 2—GROUP III

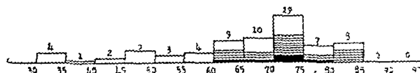
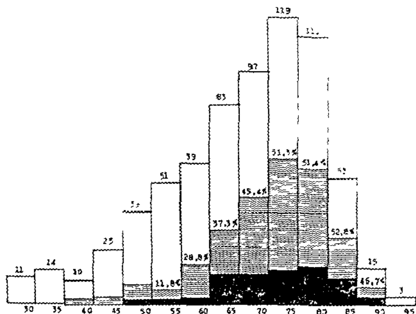


DIAGRAM 3—GROUP IV



DIAGRAMS 4—GROUP V

Diagrams 1 to 4 show distribution of the post-mortem material and the cases of Hfi on quinquenniads in the Groups II to V. The number of autopsies at the top. Black=Hfi + + and Hfi + ; streaked=Hfi + and Hfi(+). The frequency of the Hfi in per cent only in Group V.

This fact has previously been remarked upon by the present author (F. HENSCHEN, 1936, 1937). It has been mentioned before in this study that mild and even the mildest cases are "definite cases" The frequency of Hfi is, in fact, so high that in certain periods of advanced age it has been encountered in more than 50 per cent. of the series of cases the present author studied in Stockholm (Diagram 4, see ages over 70). The present series comprises a total of 390 cases of Hfi recognized at autopsy. If only Groups III and V are considered, they amount to more than 332 cases—that is, 36·9 per cent of a series including 900 autopsy cases of females over 25 years.

The diagram illustrating Group V shows that Hfi may occur even earlier than the end of the fourth decade. The incidence during this period could not be definitely established because the number of the autopsy cases available was too limited—they amounted all in all to only 65 cases of Hfi and a further case on which no autopsy was performed (p 41). Three autopsy cases of Hfi belong to the age period between 41 and 45 (p. 41). The frequency seems considerably to increase in women near the climacteric—as many as 14 cases belong to the age period between 46 and 50, *i.e.*, 2 cases of Group IV, 11 cases of Group V and 1 case of Group VI (the latter was only clinically examined) It should be mentioned that more or less pronounced endocrine disorders coexisted in a large number of cases. A clinical case of Group VI, *i e*, that of a woman aged 40, is an example rather of acromegaly than Hfi It has been included in the classification because the patient presented a typical Hfi. Many cases showed thickening and sclerosis of the skull, excessive growth of hair on the face and obesity. In numerous instances there were menstrual disorders at an early age

The diagram illustrating Group V demonstrates that the frequency of Hfi gradually increases in women over 50 and that it reaches its peak between the ages of 80 and 85 (Diagram 2. 6 of 12 cases; Diagram 3 5 of 8 cases, Diagram 4 · 52·8 per cent.). Mild cases or cases of commencing Hfi occur in each age group Severe cases before the sixth decade seem to be rare. The frequency of Hfi in the periods including the peak ages does not seem to increase, on the contrary, in the last two five-year periods which—even if the total series of cases is taken into consideration—do not comprise more than 26 cases, only 11 cases (42 per cent.) have occurred. Whether these figures imply a real decrease in frequency—possibly due to the higher death-rate in hyperostotic patients for which, among other things, hypertension might be responsible—or whether this decrease is only an apparent one has not yet been definitely recognized.

2. Behaviour of the Skull—It has not yet been possible to make a systematic study of the behaviour of the skull in the presence or absence of Hfi For the purpose of gaining—as far as it is possible—an idea of

these conditions the skull vaults were first sawn off as uniformly as possible in a series of cases of different types. After ascertaining their weights the specimens were classed light, medium-light or heavy. The skulls were then divided into sections with a band-saw, in some cases through the tuber frontale at an angle of 45° to the sagittal plane and in some transversely through the tuber parietale. The sections were then measured, photographed and X-rayed. This procedure permits not only a fair assessment of the thickness and density of the skull vaults but also of the relation between the tables and the diploe

Eighty (80 8 per cent.) of the skulls presenting Hfi were heavier than normal, 7·7 per cent. were medium-heavy and 11·5 per cent. weighed less than normal Even the weights of the skulls not affected with Hfi varied widely, *i.e.*, 46 per cent were heavy, 32·4 per cent. were medium-heavy and 21·6 per cent. weighed less than normal.

The skulls presenting Hfi set out in Group III weighed on the average 430 g In the absence of Hfi the average weight of the skulls was 345 g Similar conditions were observed in the cases of Group V.

The weights of the skull vaults in the different groups of ages show some variations above the average. In Group III the large number of heavy skulls in individuals between the ages of 46 and 50 is surprising —seven skulls weighed on the average as much as 503 g. and the maximum weight, *i e.*, 600 g., was observed in the absence of Hfi.

Obviously the great variations in the weights of the skulls are closely related to the wide variations in their thickness and density. This may be readily appreciated in sections through the tuber frontale and tuber parietale.

Even atypical forms of Hfi were rather common The two cases of Group III, which have been described in greater length, are worthy of special attention (pp 37 and 39) because they illustrate an extraordinary expansion of the new formation of bone tissue as well as transitional stages of the development towards acromegaly. Of the cases of Group V the following instances are worthy of being briefly described —

No. 1. Female aged 43, Hfi+ coexisting with numerous granule-sized osteophytes, involving the entire frontal portion of the skull, obesity, [illegible]

[illegible] the new formation of bone tissue coexisted with obesity, a cardiac [illegible]

[illegible] ed new bone formation extending to the parietal region Paralysis and hydrocephalus

No 4 Female aged 57, Hfi+, new bone formation extending to the parietal region ; slight obesity, cardiac disease and softening of the brain

No 5 Female aged 65, Hfi+, pronounced Hfi extending to the parietal region ; slight obesity, moustaches, a beard, hypertension and softening of the brain.

No 6. Female aged 68, Hfi+ + +, protuberances over the entire internal surface of the skull vault. Cancer of the breast.

No. 7. Female aged 72, Hfi+ + +, dense new bone formation even in the middle grooves of the skull; slight obesity, moustaches, a beard. Death was due to cholangitis.

No 8. Female aged 77, Hfi+ + +. The new bone formation covered the entire anterior half of the skull. Excessive obesity, moustaches, a beard, hypertension and gastric ulcer.

No. 9. Female aged 83, Hfi+ with numerous warty exostoses in the frontal region of the skull; masculine traits. Died of cardiac infarction

No. 10. Female aged 86, Hfi+ actually encroaching on the base of the skull; abnormal growth of hair on the face, senile psychosis.

Our own studies on the morphology and morphogenesis of Hfi include examinations of skulls affected with Hfi and those in which it was not present. Their thickness varied and they came from females of different ages In addition, skulls from acromegalics and pregnant women were examined

(*a*) *The X-ray Appearance of the Sections in the Presence of Hfi*—The architecture of Hfi is readily appreciated in thin sections through the skull. Figs. 16 to 37 show a representative collection of X-rays of sections of this type.

The first five sections (Figs. 16 to 20) come from skulls not affected with Hfi. They represent a variety of thick, partly sclerotic and partly porous skull vaults in which the behaviour of the tables and the diploe varies. In the films shown in Figs. 21 and 22 there is no definite evidence of Hfi. These X-rays do not differ from the other ones. In Figs. 23, 24 and 25 there is evidence of discrete though distinctly appreciable Hfi. Apart from the internal surface of the skull which appears wavy, the conditions show variations. Fig. 23 illustrates a very broad and porotic diploe and a very thin inner table. Fig. 24 shows a fairly thin diploe and a thick outer table. A characteristic of this film is the particularly thick and sclerotic inner table. Fig. 25 shows a formation of massive and porotic new bone on the still appreciable remainders of the inner table. Figs. 26 to 30 show the characteristic types of Hfi +, that is, cases of moderately pronounced hyperostosis, which can be readily distinguished. The last five X-rays (Figs. 31 to 35) illustrate very pronounced forms of Hfi which also show great variation. Figs. 32 and 33 especially show striking differences. Fig. 32 is characterized, firstly, by hyperostosis of particularly porous structure and secondly, by the complete absence of the inner table in some places. The last two films show cases of Hfi + + + in males. Here different types are represented. Fig 34 illustrates a very thick skull vault which is heavy in spite of its porosity, the vault (440 g) presenting a pronounced porous Hfi ; the inner table is not clearly recognizable.

Figs. 36 and 37 illustrate transverse sections of female skulls affected with Hfi + + + The later one is also shown in Fig. 10. The massive new bone formation as well as the absence of hyperostosis in the sagittal region is clearly visible.

(b) *The Appearance of the Frontal Bone and of Hfi under Slight Magnification*—In order to study the behaviour of the skull in general and of the tables and diploe in particular in regard to thickness, number of bone fibres and size of the marrow cavities, slightly enlarged photographs were prepared from specimens of skulls with and without Hfi (Figs. 38 to 45). This examination is considered to have definite value as a supplement to the X-ray picture.

(c) *Summary of the Histological Appearances*—A series of cases presenting different forms and degrees of new bone formation were examined. The results obtained corroborate those reported by DRESSLER, *i.e.*, the outermost layer of the dura seems to be the principal site of formation of the bony lamellæ which protrude from the internal surface of the skull vault They seem to arise in the way first reported by DRESSLER and later on by ERDHEIM Osteoblasts are hardly ever observed. In this respect we cannot concur with MOREL (see Figs. 46 to 53).

Apart from this so-to-speak characteristic Hfi formation, it may originate—though only rarely—in a manner which is strikingly similar to that in which the pregnancy osteophyte is formed (Fig. 52), that is, rows of parallel bone fibres, occasionally with distinct osteoblast borders (Fig 53) develop in the softened outermost layer of the dura Probably this type of new bone formation occurs solely if the bone is laid down particularly rapidly. DRESSLER reported that new bone formation in the shape of bone lamellæ and islands which may possibly be in contact with the internal surface of the skull frequently occur even in the intermediate and innermost layers of the dura Thus the dura is more or less incarcerated in some places and dural covering in such areas is frequently extremely thin. New bone formation involving the external surface of the skull may even occur. A discrete new formation of bone tissue consisting of very thin lamellæ is chiefly seen in skulls with a thick outer table. In some cases signs of resorption of bone were observed.

(d) *The Behaviour of the Remaining Parts of the Skull in the Presence of Hfi* was first studied on a series of skull vaults which were either thin, medium-thin or fairly thick All fairly thick skulls were examined to ascertain whether either Hed or Hfp was present In forty skulls either showing Hfi or not affected with it, transverse sections through the tuber parietale were made in the manner described, and examined Figs. 59 to 98 show the X-rays of forty sections of this type classed according to age. The variations in the thickness and density of the parietal bone are rather surprising and their exact classification gives rise to great difficulty, as in many cases they were not uniformly thickened. In some, diffuse thickening was absent though a typical Hfp was present. It should be emphasized that the thickness of the parietal bone in the sagittal region frequently differs widely from that

of the bone in the tuberal region. It is, therefore, hardly possible definitely to assess the real thickness of the parietal bone in lateral X-rays

In the following table the attempt is made to classify the forty parietal bones in regard to the thickness of the vaults and the degree of severity of the Hfi when present—

TABLE 3

Degree of Hfi	Thickness of the Parietal Bone			
	Thin	Rather Thin	Rather Thick	Thick
Absent	6	5	3	1
Hfi(+)	1	3	3	2
Hfi +	.	4	4	1
Hfi + +	1	2	1	1
Hfi + + +	..		1	1
Total	8	14	12	6

Table 3 shows that Hfi and the other forms of hyperostosis, *i e.*, Hed and Hfp, may occur more or less independently. It includes ten skulls in which, though thick or fairly thick parietal bones were present, Hfi was absent—not even traces of a commencing Hfi could be detected. On the other hand, the table shows 7 cases with appreciable or even pronounced Hfi in a thin or rather thin calvaria. In 5 cases Hfi coexisted with rather thick or even markedly thick parietal bones.

The X-rays clearly show the variations in the density of the bone. Both thin and thick bones can be either sclerotic or porous. The causes of the variations will be discussed later

Two skulls of acromegalics presenting hyperostoses of the internal surface of the skull as well as five skulls of pregnant women presenting pregnancy osteophytes were microscopically examined and compared.

(*e*) *The Microscopical Appearance of the Internal Surface of the Skull in Acromegaly* is precisely the same as that of Hfi which has just been described It is, therefore, not necessary to remark upon it in greater detail

(*f*) *The Microscopical Appearance of the Pregnancy Osteophyte*—Since the macroscopical appearance of the *processes occurring on the internal surface of the skull in pregnancy* is in the main well known, it is not necessary to refer to it here at great length In the 5 cases examined normal delivery occurred (in Case 3 Cæsarean section was performed because of heart disease, and in Cases 1, 2 and 3 the patients died of eclampsia or of heart disease on the day following delivery). The microscopical appearance in these cases was almost identical, the minor differences perhaps being explained by the fact that the new

bone formation may not have occurred or begun at the same time in all cases The internal surface of the inner table was covered by a thin and compact bony layer which continued in an inward direction as a layer of parallel rows of bone lamellæ of recent date measuring from ⅓ to ½ mm. in thickness (Figs. 54 to 58) In Case 1 there were only three rows of bone lamellæ, whereas in the 2 remaining cases they amounted to four and five respectively. In Case 1, which we consider to have been of the earliest date, fully developed layers of osteoblasts were present (Fig. 54), whereas the 2 remaining cases showed either only traces of osteoblasts (Fig. 55) or they could not be observed at all (Fig. 56).

In Cases 4 and 5 the patients did not die until some time after delivery. This caused a modification of the histological pictures. In Case 4 the patient died of septicæmia thirteen days after delivery, and the loose layer of disconnected rows of bone lamellæ was replaced by a fairly compact bone layer which had been formed through fusion of the rows of lamellæ and which showed fairly large spaces filled with loose vascular connective tissue (Fig. 57). In Case 5 the patient did not die until sixty-four days after delivery. The pregnancy osteophyte had a much more compact appearance in this case, *i e*, the five rows of bone lamellæ which had originally been present had fused to such a degree that they were marked only by parallel rows of tiny bone channels (Fig. 58). In this case the osteophyte was obviously about to be transformed into a normal internal table

In the following case the findings suggested the association of Hfi with a pregnancy osteophyte.

A female aged 30, suffering from hypertension, died in the last stage of pregnancy with cerebral symptoms

Autopsy—An almost mature fœtus (2,800 g), hypertrophy of the heart (385 g), acute cerebral hæmorrhage, weight of the skull 340 g , Hfi (?), puerperal osteophyte (?)

Microscopical Examination—The internal surface showed bone lamellæ and lines characteristic of Hfi, and at some places islands of new bone formation in the dura In addition there were in some places discrete changes similar to those seen in puerperal new bone formation Some consisted of a

In this case the histological preparations suggested the presence of a mild Hfi which at some places was overlaid by a pregnancy osteophyte, albeit poorly developed The changes due to pregnancy were by themselves too discrete to account for the appearance of the macroscopical picture in this case

(*g*) *The Behaviour of the Dura in Relation to the Vault*—In almost all cases of Hfi the dura showed the common feature of *fusing with the altered portion of the frontal bone.* In many cases a close contact

of the bone in the tuberal region. It is, therefore, hardly possible definitely to assess the real thickness of the parietal bone in lateral X-rays

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(*f*) *The Microscopical Appearance of the Pregnancy Osteophyte*—Since the macroscopical appearance of the *processes occurring on the internal surface of the skull in pregnancy* is in the main well known, it is not necessary to refer to it here at great length. In the 5 cases examined normal delivery occurred (in Case 3 Cæsarean section was performed because of heart disease, and in Cases 1, 2 and 3 the patients died of eclampsia or of heart disease on the day following delivery). The microscopical appearance in these cases was almost identical, the minor differences perhaps being explained by the fact that the new

bone formation may not have occurred or begun at the same time in all cases. The internal surface of the inner table was covered by a thin and compact bony layer which continued in an inward direction as a layer of parallel rows of bone lamellæ of recent date measuring from ⅛ to ¼ mm. in thickness (Figs. 54 to 58). In Case 1 there were only three rows of bone lamellæ, whereas in the 2 remaining cases they amounted to four and five respectively. In Case 1, which we consider to have been of the earliest date, fully developed layers of osteoblasts were present (Fig. 54), whereas the 2 remaining cases showed either only traces of osteoblasts (Fig. 55) or they could not be observed at all (Fig 56)

In Cases 4 and 5 the patients did not die until some time after delivery. This caused a modification of the histological pictures. In Case 4 the patient died of septicæmia thirteen days after delivery, and the loose layer of disconnected rows of bone lamellæ was replaced by a fairly compact bone layer which had been formed through fusion of the rows of lamellæ and which showed fairly large spaces filled with loose vascular connective tissue (Fig. 57). In Case 5 the patient did not die until sixty-four days after delivery. The pregnancy osteophyte had a much more compact appearance in this case, i.e., the five rows of bone lamellæ which had originally been present had fused to such a degree that they were marked only by parallel rows of tiny bone channels (Fig 58). In this case the osteophyte was obviously about to be transformed into a normal internal table.

In the following case the findings suggested the association of Hfi with a pregnancy osteophyte.

A female aged 30, suffering from hypertension, died in the last stage of pregnancy with cerebral symptoms

Autopsy—An almost mature fœtus (2,800 g), hypertrophy of the heart (385 g.), acute cerebral hæmorrhage, weight of the skull 340 g., Hfi (?), puerperal osteophyte (?)

Microscopical Examination—The internal surface showed bone lamellæ and lines characteristic of Hfi, and at some places islands of new bone formation in the dura. In addition there were in some places discrete changes similar to those seen in puerperal new bone formation Some consisted of a delicate, reddish and slightly calcified bone lamella lining the internal surface, and some were made up of solitary and thin bone fibres presenting osteoblasts which probably originated in the dura

In this case the histological preparations suggested the presence of a mild Hfi which at some places was overlaid by a pregnancy osteophyte, albeit poorly developed The changes due to pregnancy were by themselves too discrete to account for the appearance of the macroscopical picture in this case.

(g) *The Behaviour of the Dura in Relation to the Vault*—In almost all cases of Hfi the dura showed the common feature of *fusing with the altered portion of the frontal bone* In many cases a close contact

existed only in the area of hyperostosis; in some instances—chiefly in those with a thickened and sclerotic skull—the dura had to a more or less complete degree grown into fusion with the vault. A loose connection between the dura and the hyperostosis was seen in a few isolated cases only. This condition was particularly marked in a few cases where a brain tumour was present accompanied by chronically increased intracranial pressure.

In some instances the remaining part of the dura seemed to be more or less thickened.

3. The Condition of the Remainder of the Skeleton—*The condition of the remaining part of the skeleton* was the object of special interest. Since the females presenting hyperostosis frontalis were, as a rule, strongly built it is hardly surprising that many cases *presented a strikingly coarse skeleton. Spondylosis*—more or less pronounced—was fairly common. Its frequency was established in the cases of Group V *in both absence and presence of Hfi* It was found that of 266 cases presenting Hfi, 36·1 per cent. exhibited more or less strongly pronounced spondylosis, whereas of the 434 cases in which Hfi was absent it was present in only 21 per cent. of the cases. This striking difference is, therefore, as anticipated, in good agreement with conditions generally known

A further matter of great interest is the question *whether there is any relationship between frontal hyperostosis and senile osteoporosis.* For the purpose of ascertaining whether osteoporosis was present the skeleton was examined in numerous cases by testing the solidity of the ribs as well as the vertebral column after opening it with a broad chisel. The instrument used in testing the vertebral column was the same in all cases Of the cases presenting Hfi set out in Group III, 34·3 per cent. presented also more or less pronounced osteoporosis. In the absence of Hfi the incidence of osteoporosis was 24 per cent Corresponding and even more significant figures were computed in the cases *of Group V, i.e, 43·2* per cent. *of the cases of Hfi* were *osteoporotic,* whereas of those in which Hfi was absent only 29 per cent. showed osteoporosis Extreme osteoporosis was found in 6·4 per cent. of the cases of Hfi. In the absence of Hfi it was encountered in somewhat less than 4 per cent of the cases—a finding which likewise calls for attention.

4. Hyperostosis frontalis interna and the Structure of the Body—As early as 1937 the attempt was made to determine the structure of the body and the type of physical constitution in the presence of Hfi, although it was realized that these determinations would be extremely difficult. The material available at the time was so limited that autopsy data on the structure of the body were available in 181 cases only. Since the structure *of the body was recorded in all the cases of Group V* this series is comparatively comprehensive Their distribution is set out in Table 4 on page 65.

Figs. 16 to 35.—Sections of the frontal bone through the left tuber. Roentgenograms of Dr K. Lindblom. Nine-tenths of original size

Fig. 16.—Woman aged 61, thin sclerotic vault with digital impressions.

Fig. 17.—Woman aged 60, thick and rather porotic vault, slight Hfi, weight 335 g., no Hfi.

Fig. 18.—Woman aged 66, very sclerotic and heavy vault (515 g.), with slight Hcd: no Hfi.

Fig. 19.—Woman aged 50, rather compact and heavy vault (410 g.), with Hfp, no Hfi.

Fig. 20.—Man aged 32, thick and heavy vault with a very thick tabula externa Hcd, no Hfi.

Fig. 21.—Woman aged 44, rather heavy and thick vault, Hcd, Hfi ?

Fig. 22.—Woman aged 63, rather porotic vault, Hfi ?

Fig. 23.—Woman aged 73, rather thick and porotic vault with a thin tabula interna, Hfi +

Fig. 24.—Woman aged 69, marked thickening of the tabulæ, scanty diploe, Hfi +

Fig. 25.—Old woman, porotic Hfp with marked bone formation on the tabula interna, *Hfi +*

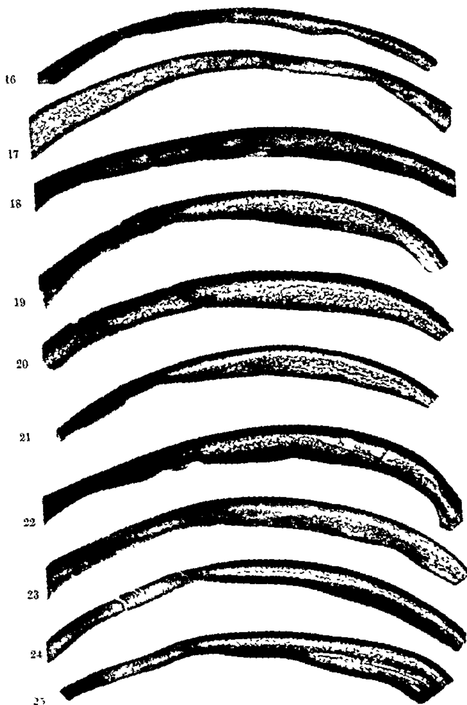

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Fig 26 —Woman aged 61, rather thin and porotic vault with an irregular tabula interna, Hfi +.

Fig. 27 —Woman aged 59, somewhat thick and dense, rather porotic vault (390 g.), Hfi +.

Fig. 28 —Woman aged 76, rather sclerotic, somewhat heavy skull (465 g.), with Hed and Hfi +.

Fig. 29.—Woman aged 76, thick and porotic vault (370 g.), Hfi +.

Fig. 30 —Woman aged 62, very thick, rather porotic, heavy vault (555 g.) with a marked tabula interna, Hfi +.

Fig. 31 —Woman aged 60, very heavy, exceedingly sclerotic vault with Hed and a very dense Hfi + +

Fig. 32.—Woman aged 74, very thick but very porotic, not heavy vault with warty and widespread Hfi + + + without distinct tabula interna.

Fig 33.—Woman aged 68, thick, sclerotic and heavy vault with a well-marked thick and porotic Hfi + + +

Fig 34 —Man aged 53, very thick and somewhat sclerotic, heavy vault (725 g.) with thick and dense tabulæ, Hfi + + +

Fig 35 —Man aged 56, not very thick somewhat sclerotic vault (440 g.) with a well-marked older tabula interna and a warty and porous Hfi + + + without marked newer tabula.

PLATE V

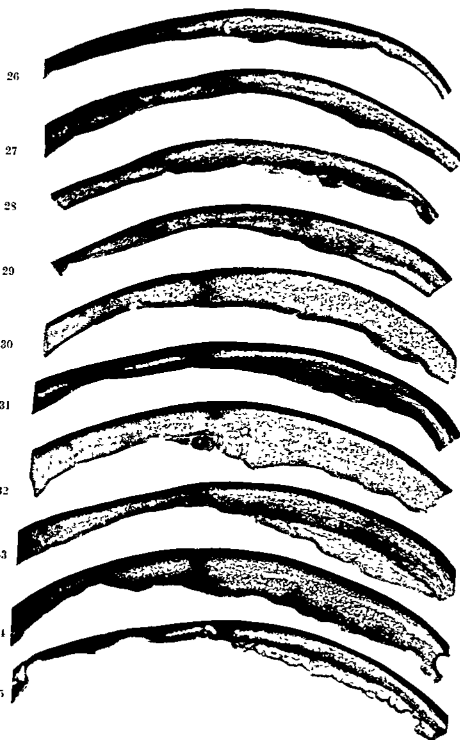


Fig. 36.—Transversal section through the frontal bone of the very thick, slightly sclerotic and heavy vault of a woman aged 65, with marked persistent older tabula interna and Hfi of very high degree Nine-tenths of original size.

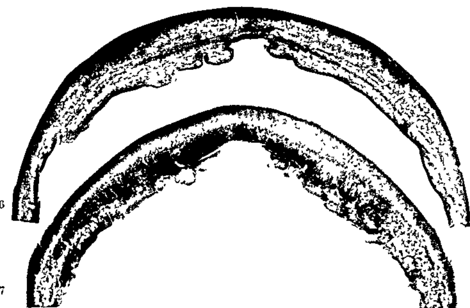
Fig. 37.—Transversal section through the frontal bone of the very thick and rather compact vault (550 g) from a woman aged 74, with enormous sclerotic Hfi. *Cf.* Fig 10. Nine-tenths of original size

Figs. 38 to 45—Sections from calvariæ of old women Magnification, *circa* 3 ×

Fig. 38.—Sclerotic, somewhat thick calvaria with very thick tabulæ and a dense diploe, Hfp, no Hfi.

Fig. 39—Thick and very porotic calvaria with thin tabulæ and a spongious diploe.

Fig. 40.—Thick, somewhat sclerotic calvaria, with a thin tabula interna, Hfi + +; no remains of the original tabula interna.



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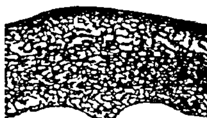

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FIG. 41.—Thin calvaria with a warty, somewhat sclerotic Hfi + +

FIG. 42.—The inner half of a calvaria with big hyperostotic warts, partly sclerotic, partly very porotic, Hfi + + +.

FIG. 43.—Islets of new bone in the dura, with secondary confluence with the inner surface of the frontal bone, Hfi + +

FIG. 44.—Calvaria of rather normal thickness, with Hfi of very high degree (+ + +) The position of the primary tabula interna is still visible.

FIG. 45.—Enormous and irregular Hfi + + +, partly very sclerotic, partly porotic

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FIGS. 46 to 53.—Slides from the inner surface of six calvariæ with Hfi.

FIG. 46.—Thin layer of new bone with very well-marked cement lines forming a flat protuberance, the border of the bone apposition lies in the left margin of the Fig. Magnification, *circa* 10 ×.

FIG. 47.—Apposition of new bone with numerous fine cement lines. To the right a very thin layer of new bone. Magnification, *circa* 10 ×

FIG. 48.—Bone apposition of higher degree with irregular thicker or thinner lamellæ and marked cement lines A Volkmann canal interrupts the system of lamellæ and cement lines. Magnification, *circa* 10 ×.

FIG. 49.—Formation of flat-warty bone islets in the dura, with secondary fusion with the old bone Between the old and new bone there are included fibres of the dura



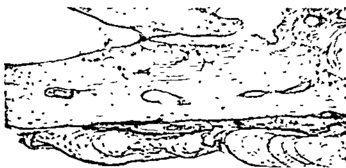
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FIG. 50.—A great warty exostosis on the inner surface of the calvaria in a case of Hfi. The central parts are composed of bone tissue from an earlier apposition. The superficial layers are more recent, and show marked cement lines. Magnification, *circa*, 7 ×.

FIG. 51.—Abundant formation of new bone in the shape of bigger and smaller warts with thicker or thinner bone lamellæ and arched cement lines. Magnification, *circa* 15 ×.

FIG. 52.—From the internal surface of the calvaria of a woman aged 77, with Hfi and adiposity. Below: the dura with some rows of new bone lamellæ, very similar to the bone formation in the pregnancy osteophyte. In the middle: bone lamellæ and cement lines as in typical Hfi bone. Above: older bone tissue. Magnification, *circa* 20 ×.

FIG. 53.—The same case as in Fig. 52, high power. Below: [illegible] a new b[illegible] sides. [illegible] Magnific[illegible]

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FIGS. 54 to 58.—Slides from the inner surface of the calvaria with the pregnancy osteophyte in diverse phases of development. Magnification, *circa* 20 ×.

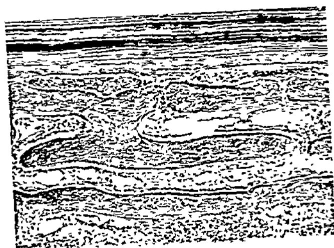
FIG 54 —From a woman aged 28, who died one day after a delivery at the right date Three rows of thick bone lamellæ with osteoblasts.

FIG. 55 —From a woman aged 37, who died one day after a delivery at the right date. Five rows of somewhat thinner bone lamellæ, traces of osteoblasts.

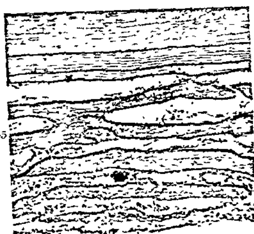
FIG. 56.—From a woman aged 38, who died one day after a Cæsarean section at the right time Four or five rows of bone lamellæ without distinct osteoblasts.

FIG 57 —From a woman aged 22, who died thirteen days after a delivery at the right time. The earlier three- or four bone lamellæ have already flowed together. Above, numerous very thin and regular lamellæ and cement lines.

FIG. 58 —From a woman aged 31, who died sixty-four days after a delivery at the right time Advanced fusion of the five earlier bone lamellæ, their outlines still marked by narrow bone channels.



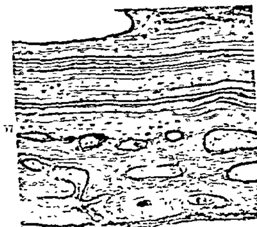
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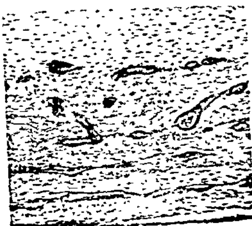
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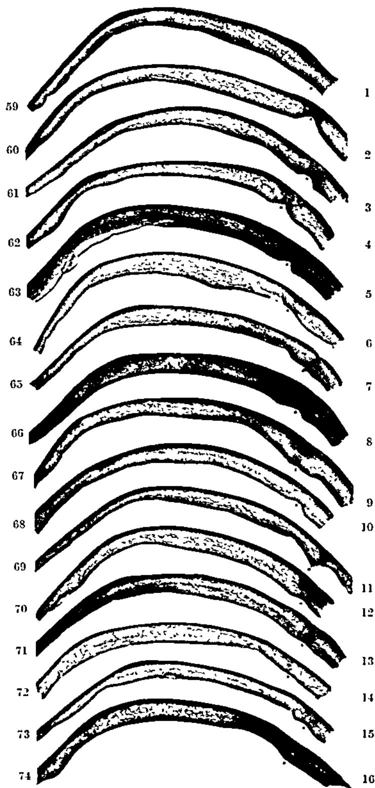
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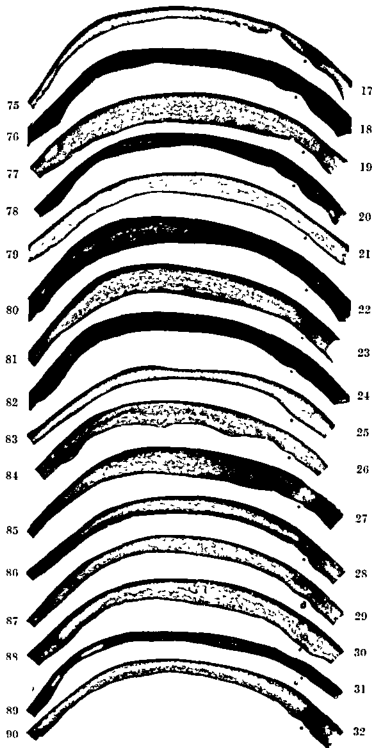


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FIGS. 91 to 98. Eight Roentgenograms of transversal sections of the left parietal bone through the parietal tuber, the sagittal line being marked by a point. From women aged 73 to 86 years. Description of the figures in the text, pp. 61 and 62. Roentgenograms of Dr K. Lindblom. Three-quarters of original size.

FIG. 99.—The skull of an old woman of the Norwegian Iron Age (the Oseberg ship) seen from behind and showing a typical Hfi of lower degree (p. 164). Three quarters size of the original photo of Professor K. E. Schreiner of Oslo

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TABLE 4

Hfi	Number of Cases	Delicate	Rather Strong	Strong
With . .	84	1	41	42
Without . .	97	20	66	11
Total .	181	21	107	53

The figures indicate that a shift of the type of physical constitution from the delicate to the strongly built occurred concurrently with the development of Hfi. In Group V the cases have been classified as delicate, rather strong, pyknic or strong. The following table shows the distribution of this series in terms of percentage values :—

TABLE 5

Hfi	Delicate	Rather Strong	Pyknic	Strong
	per cent.	per cent.	per cent.	per cent.
With . .	12 1	62 0	15·3	10·6
Without . .	22 0	62·8	8 7	6 5

In Table 5 the trend of the figures is even more clearly appreciable. The number of cases classed "rather strong" does not show any changes, whereas that of those assessed "delicate" has considerably decreased. On the other hand, the number of cases classed "pyknic" and "strong" has increased.

Graphically expressed, the trend of these figures has the following appearance :—

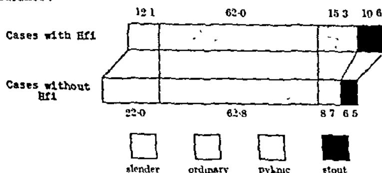


DIAGRAM 5

"Displacement" of the constitutional type in the cases with Hfi from more slender to more stout Reduction of the frequency of the slender type corresponding to an augmentation of the pyknic and the stout types.

What this "shift" actually implies—whether it expresses a real modification of the physical constitution due to the factor responsible for the origin of Hfi or whether it is caused by the fact that this factor is less frequently operative in delicately built women than in pyknic and strongly built women—will be discussed elsewhere in this book.

Special attention was given to the occurrence of a broad and coarse face and masculine traits. Of the 84 cases of Hfi of Group III the face showed more or less pronounced masculine traits in 18 instances, 19 of the 700 cases of Group V presented a coarse and masculine face. Fourteen were cases of Hfi and in 5 Hfi was absent—expressed in terms of percentage this is equal to 5·3 per cent. and 1·2 per cent. respectively.

In this connection it should be mentioned that the present series of cases was very homogeneous in regard to "race." In some cases there was probably some percentage of Walloon blood, which is fairly common in Sweden, particularly in middle Sweden. The whole series included extremely few women of definitely alien race, *i.e.*, one Russian woman and a few Jewesses.

5. Incidence of Morgagni's Syndrome in its Complete Form.—From what has been said it is clear that the frequency of Hfi is very high. This, however, does not imply that Morgagni's syndrome in its complete form was present in all cases. It was found in about half of the cases presenting Hfi set out in Group V.

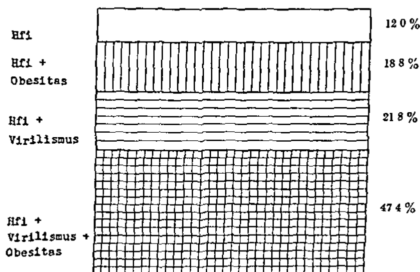


DIAGRAM 6

Distribution of four categories of Hfi cases in Group V
Virilismus mostly means hirsutismus

Diagram 6 shows that Morgagni's triad in its complete form was found in only 47·4 per cent. of the total of 266 cases presenting Hfi; in

more than one-fifth—that is 21·8 per cent.—Hfi was solely associated with virilism, and in roughly one-fifth—that is 18 8 per cent.—Hfi coexisted with obesity. Finally, in 12 per cent. of the cases Hfi was present alone.

Even in the presence of the complete triad the degree of severity of its different components varied considerably. Apart from examples of genuine and fully developed MS coexisting with the severest forms of Hfi—abnormal growth of hair on the face, coarse appearance, large hands and feet and extreme obesity—there were numerous cases in which one or two of the components were only weakly pronounced. By measuring the different degrees of severity of each component on a point basis up to a maximum of 4 points the attempt was made to record the frequency of the different degrees of severity of MS in the form of a graph.

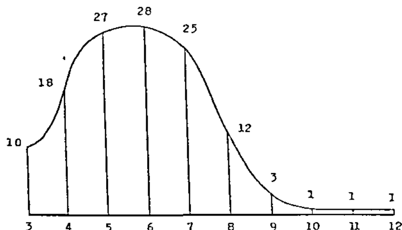


DIAGRAM 7

Distribution of the cases with complete MS in Group V by points

Diagram 7 shows that the cases given from 5 to 7 points, that is, cases of Hfi+, associated with virilism ++, obesity ++ or, say, Hfi+++, virilism +, obesity +++, preponderated numerically (80 cases), whereas extreme cases of MS in its complete form with highly pronounced Hfi, very pronounced virilism and extreme obesity, that is, the cases given from 10 to 12 points, were extremely rare; only one case of each was represented.

6. Constitutional Abnormalities in the Absence of Hfi—Since the data on the 700 cases of Group V are in many respects very reliable, the examination on the constitutional conditions could be extended even to the cases not affected by Hfi. The instances presenting virilism associated with obesity, though in the absence of Hfi, as well as the cases manifesting either solely virilism or solely obesity were also taken into consideration. Diagram 8 shows the incidence of the

different associations. The group in which association of virilism with obesity is set out is worthy of special consideration because it is a very common constitutional abnormality. Italian authors termed it "piccolo Cushing," and GELLERSTEDT "cushingoid habitus." This group includes even several cases of pronounced Cushing's syndrome.

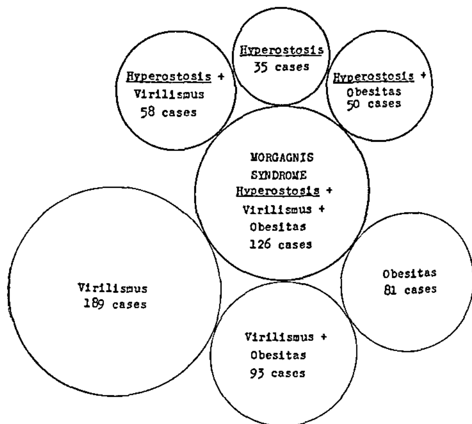


DIAGRAM 8

Frequency of the complete and incomplete MS in Group V. Frequency of kindred conditions in the same group Virilismus mostly means hirsutismus.

7. Growth of Hair on the Face—When the degree of hair-growth on the face was tabulated the mildest forms of hypertrichosis were even taken into consideration. This explains the high figures obtained—it may even be said that they are surprisingly high. The presence of moustaches alone or of a beard alone as well as of particularly thick eyebrows was likewise recorded. It was extremely difficult definitely to assess these conditions because excessive growth of hair on the upper lip, chin and the cheeks had been removed by depilation in many cases. Since excessive growth of hair is, no doubt, frequently artificially removed, our figures may be considered to express the minimum

percentage of incidence of hypertrichosis An excessively growing beard was fairly often cut short with a pair of scissors.

In Group III the degree of hair-growth on the face was recorded in a total of 184 cases. One-quarter of the cases not presenting Hfi shows appreciable hairiness of the face, whereas the remaining three-quarters of the cases are devoid of hair. Even pronounced hairiness was observed (2 cases). The majority of the 74 cases of Hfi (48) showed distinct hairiness—in 31 it was moderate and in 17 it was pronounced, whereas 26 cases were either devoid of hair or manifested lanugo only. *The correlation is particularly distinct in the presence of hyperostosis of severer degrees,* say, of hyperostosis ++ and +++. Only 3 were devoid of hair, whereas in 26 instances there was definite abnormal growth of hair—in 11 of these cases it was extremely pronounced and involved a fairly large area.

TABLE 6

Degree of Hyperostosis	Number of Cases	Hairiness of the Face			
		Absent or Traces	Present	Distinct	Pronounced
Negative . .	110	84	26	23	3
Positive . .	74	26	48	31	17
Total	184	110	74	54	20
Out of these—					
(+) . .	13	7	6	4	2
+ . .	32	16	16	12	4
++ .	16	2	14	10	4
+++ . .	13	1	12	5	7

Table 7 demonstrates that it is possible, though with some reserve, to infer the presence of Hfi from the degree of hairiness of the face. Exceptions, however, are fairly frequent. Of 74 cases, 48 showed abnormal hairiness of the face associated with marked hyperostosis. Of 20 cases as many as 17 were examples of abundant growth of hair on the face concomitant with hyperostosis.

TABLE 7

Degree of Hairiness	Number of Cases	Degree of Frontal Hyperostosis					
		Negative	Positive	(+)	+	++	+++
Distinct	54	23	31	4	12	10	5
Pronounced	20	3	17	2	4	4	7
Total .	74	26	48	6	16	14	12

When determining the correlation between Hfi and abnormal growth of hair on the face in the cases of Group V, the following figures were obtained :—

TABLE 8

Degree of Hfi	Number of Cases	Negative	Positive	Distinct	Pro-nounced
Negative .	426	222 = 52·1%	204 = 47·9%	166	38
Positive .	263	81 = 30 8%	182 = 69·2%	122	60
Out of these—					
(+) . .	63	25 = 39·7%	38 = 60·3%	26	12
+ . .	123	36 = 29 3%	87 = 70 7%	62	25
+ + . .	48	12 = 25 0%	36 = 75·0%	23	13
+ + + .	29	8 = 27 6%	21 = 72·4%	11	10

If the correlation is expressed in terms of percentage instead of in figures, the difference between the cases with Hfi and those in which *Hfi is absent becomes still more distinct. Fifty-two per cent. of the cases not affected with Hfi showed "normal" hairiness of the face*—assessed according to our standard—whereas of the cases presenting Hfi, only 30·8 per cent. showed "normal" hairiness and in 69·2 per cent. hair-growth was abnormal Whether there was any relationship between the different degrees of severity of Hfi and the incidence and degree of growth of hair on the face cannot be definitely stated because the number of cases in most of the groups is too limited.

8. Axillary Hair-growth—The growth of hair in the axillæ and the pubic region was also tabulated. It is well known that the hair of the axillæ becomes either scanty or disappears completely in elderly women We therefore first investigated these conditions in unselected cases and found the following —

TABLE 9

Females	Age					
	21 to 40	41 to 50	51 to 60	61 to 70	71 to 80	81 to 90
Scanty or no axillary hair	1 = 2 5%	9 = 16 4%	40 = 37%	99 = 59%	174 = 77%	54 = 75%
Normal axillary hair	39 = 97·5%	46 = 83 6%	68 = 63%	70 = 41%	52 = 23%	18 = 25%

Table 9 shows that growth of hair in the axillæ decreases progressively with age in women The figures covering the peak age period would probably have expressed this decrease even more significantly if more cases had been available. The following table shows the correlation between Hfi and either scanty or absent axillary hair .—

TABLE 10

Hfi	Axillæ	Age				
		35 to 50	51 to 60	61 to 70	71 to 80	81 to 95
Females with	Scanty hair or devoid of hair	2	13	41 = 60%	88 = 77·2%	30
	Normal hair-growth	12	9	28 = 40%	26 = 22 8%	5
Females without	Scanty hair or devoid of hair	8	28	57 = 56·7%	85 = 76 2%	23
	Normal hair-growth	43	59	40 = 43 3	26 = 23 8%	12

Table 10 demonstrates that the frequency of scanty axillary hair or lack of axillary hair is hardly any higher in women with Hfi than in those without Hfi. It further shows that the difference expressed in terms of percentage between normal axillary hair-growth and scanty or absent axillary hair in females, whether afflicted with Hfi or not, is too slight—at least in the age period 61 to 70 and 71 to 80, which include a comparatively large number of cases—to permit the definite conclusion that a correlation between Hfi and axillary growth of hair exists. Percentage figures have not been calculated on the other decades owing to the limited number of cases represented on each.

9. Hfi and General Nutritional State—Among the conditions to which special attention was given in the present study is included the general nutritional state of the patients. In the first place the subcutaneous deposition of fat in general was examined and, in addition, attention was directed to any localized abnormality (breasts, hips, extremities, abdominal viscera and so forth). It should be mentioned that the incidence of extreme obesity in elderly women—which eight or ten years ago was still high among the autopsy cases of St Erik's Hospital in Stockholm—has gradually decreased in the last years. This is probably either due to propaganda for an adequate diet and intensification of physical exercise or the type of patients and diseases treated at the hospital may have changed

As it was soon discovered that frontal hyperostosis was associated with general obesity of more or less severe degree in many cases, the general nutritional state of the individuals examined was—as far as it was possible—systematically examined and classified as follows: Very fat, moderately fat, thin and very thin. This classification encountered some difficulty, chiefly because it was often not possible to differentiate the cases showing either acute or recent loss of weight.

When determining the correlation between Hfi and abnormal growth of hair on the face in the cases of Group V, the following figures were obtained :—

TABLE 8

Degree of Hfi	Number of Cases	Negative	Positive	Distinct	Pro-nounced
Negative .	426	222 = 52·1%	204 = 47·9%	166	38
Positive .	263	81 = 30 8%	182 = 69·2%	122	60
Out of these—					
(+) . .	63	25 = 39 7%	38 = 60·3%	26	12
+ . .	123	36 = 29·3%	87 = 70 7%	62	25
+ + . .	48	12 = 25 0%	36 = 75 0%	23	13
+ + +	29	8 = 27·6%	21 = 72 4%	11	10

If the correlation is expressed in terms of percentage instead of in figures, the difference between the cases with Hfi and those in which Hfi is absent becomes still more distinct. Fifty-two per cent. of the cases not affected with Hfi showed "normal" hairiness of the face—assessed according to our standard—whereas of the cases presenting Hfi, only 30·8 per cent. showed "normal" hairiness and in 69·2 per cent. hair-growth was abnormal. Whether there was any relationship between the different degrees of severity of Hfi and the incidence and degree of growth of hair on the face cannot be definitely stated because the number of cases in most of the groups is too limited.

8. **Axillary Hair-growth**—The growth of hair in the axillæ and the pubic region was also tabulated. It is well known that the hair of the axillæ becomes either scanty or disappears completely in elderly women. We therefore first investigated these conditions in unselected cases and found the following .—

TABLE 9

Females	Age					
	21 to 40	41 to 50	51 to 60	61 to 70	71 to 80	81 to 90
Scanty or no axillary hair	1 = 2 5%	9 = 16 4%	40 = 37%	99 = 59%	174 = 77%	54 = 75%
Normal axillary hair	39 = 97 5%	46 = 83 6%	68 = 63%	70 = 41%	52 = 23%	18 = 25%

Table 9 shows that growth of hair in the axillæ decreases progressively with age in women The figures covering the peak age period would probably have expressed this decrease even more significantly if more cases had been available. The following table shows the correlation between Hfi and either scanty or absent axillary hair :—

correlation was even here definite becomes particularly clear if the cases set out at the top of the table on the right, and in which there was a history of incidental loss of weight of unknown reason, are excluded.

TABLE 12

Degree of Hfi	Extremely Fat	Very Fat	Fat	Somewhat Fat	Moderate	Somewhat Thin	Thin	Extremely Thin	Total
Hyperostosis + + +	2	1	16	10	3	1	...	2	29
Hyperostosis + + .	3	13	10	10	9	3	.	1	49
Hyperostosis + .	1	11	37	29	29	6	11	1	125
Hyperostosis (+) .	1	5	18	16	9	9	5	.	63
Without hyperostosis	..	20	65	91	98	50	30	19	373
Total .	7	50	140	156	148	69	46	23	639

10. The Brain in Cases of Hfi—It is well known that senile atrophy of the brain is, as a rule, much more pronounced in women than in men of the same age. For this reason, and because numerous authors claimed that a relationship existed between *Hfi* and various more or less pronounced manifestations of psychiatric and neurological character, it was considered necessary to find out if evidence could be brought forward in support of a relation between anatomically demonstrable alterations of the brain, particularly atrophy of the brain, and Hfi. The average weights of the brains in the absence and presence of Hfi of the cases classed in Group III are set out in the following table :—

TABLE 13

	Cases without Hfi	Dubious Cases	Cases with Hfi
Number of cases	67	11	55
Average weight	1,254g.	1,217g	1,202g

The figures set out in the following table indicate the distribution of the brains in the different decades in the presence and absence of Hfi :—

TABLE 14

Hfi	Age in Years				
	41 to 50	51 to 60	61 to 70	71 to 80	81 to 90
Without .	1,335	1,282	1,231	1,209	1,133
With	1,342	1,290	1,200	1,207	1,130

The figures referring to the cases of Group III set out in Table 11, therefore, should be considered with some reserve.

TABLE 11

Degree of Hfi	Very Fat	Fat	Somewhat Fat	Moderate Nutritional State	Thin	Very Thin	Total
Without .	3	12	21	34	28	17	115
With .	18	30	15	18	7	3	91
Total .	21	42	36	52	35	20	206
Out of these—with ++ or +++	15	16	2	6	3	1	43

As may be seen, the distribution in the six groups indicated in this table is closely related to the presence or absence of Hfi. *This relationship can be clearly appreciated by studying the distribution of the cases manifesting either pronounced or very pronounced hyperostosis in the different groups indicating the nutritional state.* In graphic form and expressed in terms of percentage the distribution in the presence and absence of hyperostosis has the following appearance:—

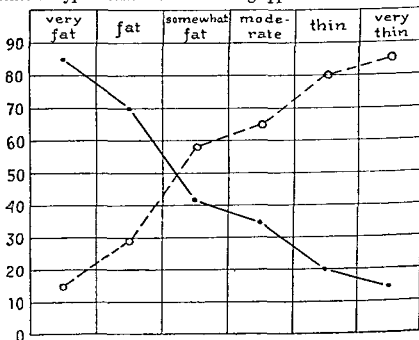


DIAGRAM 9

Nutritional state and Hfi expressed in percentage. The statistics comprise 206 cases, *i e.*, 91 with Hfi (———) and 115 without Hfi (– – – –).

The figures indicating the correlation between Hfi and obesity in the series of cases classed in Group V are set out in Table 12. That the

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Hyperostosis + + .	3	13	10	10	9	3	..	1	49
Hyperostosis + .	1	11	37	29	29	6	11	1	125
Hyperostosis (+) .	1	5	18	16	9	9	5	.	63
Without hyperostosis	.	20	65	91	98	50	30	19	373
Total .	*7*	*50*	*140*	*158*	*148*	*69*	*46*	*23*	*639*

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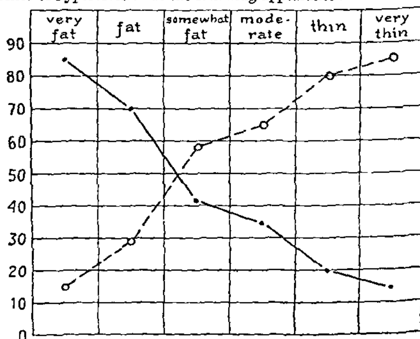


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slowly, will give rise to clinical manifestations. This matter will be treated at greater length later on in this book.

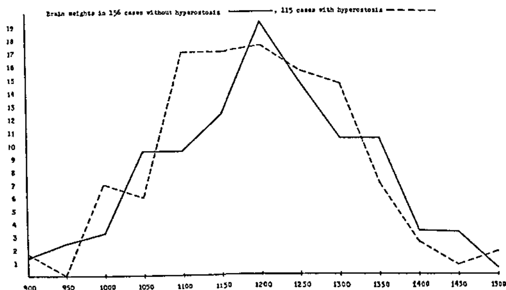


DIAGRAM 10

Distribution curve of the brain weights in 156 cases without Hfi (———) and 115 cases with Hfi (- - - -). Number of the cases to the left, brain weights below.

11. The Heart in Morgagni's Syndrome—It has long been well known that obese and elderly women often manifest symptoms of hypertension and cardiac trouble. Since the series classed in Group V was comparatively comprehensive, the behaviour of the heart and of the blood vessels in the cases presenting Hfi of this group was examined As the weights of the hearts were systematically determined at the post-mortem examination in all cases the figures obtained give a clear idea of these conditions. Naturally all cases were excluded in which causes may have accounted for the hypertrophy of the heart, such as valvular diseases—whether of endocarditic, luetic or arteriosclerotic origin—and certain cases of pericardial adhesions, thyrotoxicosis and chronic interstitial nephritis Even cases of right-sided hypertrophy of the heart were excluded The cases were divided into three groups, viz., Group I, including the cases which were not fat, Group II comprising the cases classed as fat; Group III, in which the cases of MS were distributed. The differences in the weights of the hearts are indicated in terms of 50 g. The distribution curves indicated in Diagram 11 were constructed in this manner.

It will be appreciated that the curve expressing the weight of the hearts of the females classed "not fat" is the lowest one. On post-mortem examinations of Swedish-born subjects it has been found that

These figures clearly illustrate the gradual decrease in the weights of the brains. *On the other hand, the presence or absence of Hfi is not reflected by changes in the average weights of the brains.* They were surprisingly small in the absence as well as in the presence of Hfi. The brain of a woman aged 82 with Hfi + + + weighed only 900 g., that of a woman aged 62 with Hfi + + weighed 1,075 g. In other cases of very pronounced Hfi, e g., in Case 100 which was that of a woman aged 82 with Hfi + + + and whose skull weighed 450 g., the brain weighed 1,250 g. The brain of another woman aged 65 with Hfi + + weighed 1,450 g., and so forth. On the other hand, *numerous cases of considerable atrophy of the brain were encountered in which hyperostosis was completely absent, e.g.*, the brain of a well-fed woman aged 68 weighed 950 g. In the case of a female which was not included in this series, who was 77 years old, extremely thin and exhibiting senile dementia, the brain also weighed 950 g. In a series of cases in which Hfi was absent the weight of the brain varied between 1,000 and 1,100 g.

Similar results were obtained when tabulating the weights of the brains of the cases included in Group V (700 cases).

TABLE 15

Degree of Hfi	Age in Years				
	41 to 50	51 to 60	61 to 70	71 to 80	81 to 90
	g.	g.	g.	g.	g.
Without .	1,260	1,248	1,239	1,166	1,085
With	1,292	1,239	1,224	1,162	1,141
With + + and + + +	1,172	1,247	1,182	1,138	1,131

The curves expressing the distribution of the weights of the brains in the absence and presence of Hfi illustrate these conditions even more clearly (Diagram 10). The differences—if they exist at all—are so slight that in my opinion they do not help to throw any light on the pathogenesis of Hfi.

Apart from this senile atrophy, which frequently occurred in the presence as well as in the absence of Hfi, we fairly often observed—though only in the presence of extreme forms of Hfi and in which pronounced atrophy of the brain was absent—*a localized facet-like flattening of the frontal lobe. This localized alteration in the shape of the brain* which MORGAGNI mentioned as early as 1719 · " . . . introrsum protuberant, ac cerebrum comprimebant," *appears to be the more marked the less pronounced the general atrophy of the brain is.* We interpret it as a reflection of the power of accommodation on the part of the brain, a property which in the presence of an atrophic brain is generally not demanded. It is not likely that this process of compression involving the frontal lobe, and which progresses extremely

actually completely absent. In a larger number they were often practically only present anteriorly and below. It should be mentioned, however, that a decrease in the number of Cc's was demonstrated in the majority of obese and elderly women Apart from the above-mentioned cases of adenoma they were present in large quantities in only one case of Hfi.

The *Ac's showed a more or less considerable increase* in the presence of Hfi. In numerous instances they were present in large and compact groups, which were chiefly symmetrically arranged and resembled an adenoma. A true encapsulated adenoma was not found. The increase of Ac's was particularly obvious in the case of a woman aged 82 presenting hyperostosis + + + coexisting with abnormal growth of hair and obesity.

The Bc's were also strikingly increased in the great majority of the cases They were often seen in the shape of voluminous and compact groups, suggesting an adenoma. A true adenoma with a capsule was not observed. In some cases there was a moderate overgrowth of Bc's. In the cases in which Hfi was absent but which manifested adiposity, basophilism was roughly just as pronounced as in those in which Hfi was present. Basophilism was observed, even in a few women classed " thin " and manifesting Hfi.

In other respects the behaviour of the hypophysis—at least as far as is known up to date—does not seem to be a matter of great interest. A large number of cases either affected or not affected with Hfi showed marked sclerosis of the anterior lobe. In the case of the above-mentioned female aged 82 presenting very pronounced Hfi, and in Case 4 (p 53), the increase and hyaline sclerosis of the stroma were particularly marked. Passing mention should be made of the so-called basophilic infiltration of the neurohypophysis as well as intermediary groups of cells and cysts and groups of the so-called fœtal cells which were frequently found.

The neurohypophysis was particularly rich in fibres and more vividly pigmented than normal in many cases—in both absence and presence of Hfi.

Thus *the microscopical examination of the hypophysis revealed conditions which seem—to a certain extent—to depart from the normal,* such as increase of the Ac's and particularly of the Bc's, which in our opinion, however, do not permit any definite conclusions. On the other hand, these findings support the major importance of a careful quantitative microanalysis of the human hypophysis. If this is made " subjectively " only it will hardly be possible to carry elucidation of the morphology of the frontal hypophyseal lobe a step further. Our suggestions led FLODERUS to make a careful quantitative examination of the cytological conditions in the frontal lobe of the hypophysis in men. We shall revert to this matter later on in this book.

the hearts generally weighed approximately 325 g. Our findings are in agreement with this. The curve expressing the weights of the hearts in stout females is on the average 75 g. higher, *i.e.*, its peak lies at 400 g. Finally, it may be seen that in the majority of the cases of MS the hearts weigh even more, because the peak of the distribution curve lies at 450 g.—more precisely, it is approximately 125 g. higher than that indicating the weights of the hearts in the cases classed "not fat." The conclusions which may be drawn from these figures will be discussed elsewhere in this book.

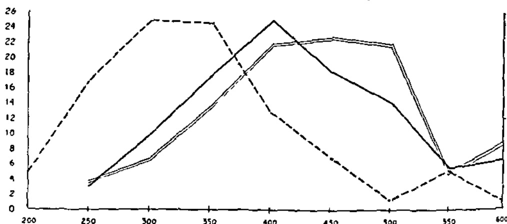


DIAGRAM 11

Distribution curve of the heart weights in females without obesity (----), and in all fat females (———), and in cases with MS (═══). Number of the cases to the left, heart weights below.

12. The Behaviour of the Endocrine Organs—For various reasons it has so far not been possible to make systematic macroscopical and microscopical examinations of these organs, nevertheless we feel that our investigations helped in throwing some light on their behaviour in the presence of Hfi.

Hypophysis—X-ray examination of the sella was made in a few isolated cases only. In Case 83 of Group III, in which acromegaly coexisted with MS, the sella was balloon-shaped; it measured *13 × 13 mm., and its lower borders were not clearly defined. Autopsy* revealed a fairly large chromophobe adenoma at the base of the brain. In the peculiar case of Group VI (p. 41), which likewise manifested a complex endocrine disorder, the sella measured 14 × 11 mm. This patient was still alive at the time of writing.

Macroscopically, the hypophysis did not show any changes (with the exception of Case 2, p 51). On *microscopical examination* of the hypophysis in females—which was made on a large scale only on the cases of Group III—*a marked decrease in the relative number of the Cc's was found in all cases of Hfi.* In a fairly large number they were

the general physical constitution of the patient resembled that of other members of the same family or that several members of one and the same family had died of the same disease—*e g*, of "apoplexy" or "cerebral hæmorrhage"

We centred our interest on the data concerning *menstruation* and *pregnancy* in the past histories Particular attention was given to pregnancy because the initial stage of Hfi undoubtedly bears some resemblance to the pregnancy osteophyte formation.

The observations made on our series of cases support the view that *hyperostosis frontalis develops independently of pregnancy*. Both the age of the patients and the fact that hyperostosis may occur in cases of definite nulliparæ rule out the possibility of a direct correlation between the two conditions.

Many of our cases of Hfi were women who had never had any children. Unfortunately the difficulties in the way of determining their exact number were great; in particular, that of the women who had never been pregnant could not be definitely ascertained. It may, however, be assumed that they represent roughly one-quarter to one-third of our series. This applies to Groups III and V.

Two facts, however, have been definitely recognized—i e, *hyperostosis frontalis in its severest forms may occur in cases of definite nulliparæ and on the other hand may be absent in multiparæ.* Thus it is clear that there *does not exist any direct relation between Hfi and the so-called pregnancy osteophyte*. This, however, does not imply that the development of Hfi directly on the basis of a pregnancy osteophyte in a comparatively young woman—as was the case in Case 1 of Group IV, for instance—is an extremely rare exception

2 **Hypertension**—One of the few symptoms frequently manifested in our series of cases was increase of blood pressure. The past histories and the clinical reports contained data on this manifestation in a large number of the cases. On the other hand, many patients were moribund when admitted to hospital and frequently their blood pressure had decreased to such an extent that it could not be measured. When determining the actual blood pressure in the cases of Group V we therefore considered the weights of the hearts determined at the post-mortem examinations in addition to the clinical data. Naturally, cases of cardiac diseases and so forth were excluded. The graph of the weights of the hearts and of the values of the systolic blood pressure in our cases of severe and extreme Hfi—from which cases of cardiac diseases were eliminated—indicates (Diagram 12, p. 80) that cardiac hypertrophy and hypertension obviously predominated Apart from 11 cases with hearts of approximately normal weights, the hearts were either too heavy or the values of the blood pressure too high, or both conditions coexisted.

The Parathyroids—No noteworthy alterations were disclosed. The usual groups of transparent and large acidophilic cells, which are almost always present in elderly individuals, were found in almost all cases examined.

Thyroid Gland—Again no particularly noteworthy alterations were found. An adenoma rich in colloid or a slight adenomatous colloid goitre was present in a fairly large number of cases. In many instances the thyroid gland showed senile atrophy and was also poor in colloid. True cases of thyrotoxicosis were not encountered

Suprarenal Glands—The picture of the adrenal glands showed great variations. In many instances the principal disease—that is, the disease which called for medical advice—accounted for them. In this connection it should be mentioned that particular or remarkable alterations in the form of cortical hyperplasia or cortical adenoma were not demonstrable in the cases presenting abundant and abnormal growth of hair on the face. The cytological alterations of the suprarenal glands and their importance will be discussed later on in the present book.

Ovaries—The microscopical picture of the ovaries was comparable with that usually seen in senile atrophy and sclerosis. In a fairly large number of the cases affected and not affected with Hfi there were ovaria gyrata. Extremely severe atrophy was occasionally present in elderly individuals. Sometimes various kinds of solitary cysts were seen.

Pancreas—In accordance with the general adiposity lipomatosis of the pancreas was present in a large number of the cases. Frequently, also, general and senile atrophy was encountered. In some cases the pancreas was microscopically examined because diabetes had been recognized clinically.

As regards the *other internal organs* there was nothing noteworthy. Neither in elderly nor very old women did the conditions depart from the normal ones. The incidence of atrophy of the organs, brown pigmentation and arteriosclerosis was the same in all cases

The Clinical Picture of Morgagni's Syndrome and Hyperostosis frontalis—As was mentioned before, the cases classed in Group V manifested a variety of *clinical symptoms*. The attempt was made to single out the essential clinical manifestations in the case histories. To this end the total series of cases presenting Hfi—that is, 266 cases—as well as the 76 cases of severe and extreme Hfi were considered in the compilation. It is always specially indicated to which of the two groups the compiled data refer

1. Past History—No hereditary or familial conditions which might have had a bearing on the problems discussed in this book were disclosed. In not one of the instances examined were two members of the same family affected with Hfi. In a few cases there was a history that

not possible to study the minor disorders of carbohydrate metabolism in the majority of the cases because the relevant data were incomplete. The instances in which the blood-sugar content was less than 110 to 115 mg. per cent. and the urine negative for sugar (Almén and Benedict) were therefore considered negative cases, and those in which the urine was positive for sugar and the blood sugar elevated as well as the cases merely referred to as cases of diabetes in the histories, were classed as positive cases. Although we are fully aware that this classification implies a comparatively great simplification and generalization, we feel that it nevertheless helped to shed some light on the frequency of the coexistence of disorders of the carbohydrate metabolism and MS.

Hfi and Disorders of the Carbohydrate Metabolism—Clinical data on the behaviour of the blood sugar and sugar content of the urine were available in only 233 of the 266 cases of Hfi. Of the 434 cases in which Hfi was absent the data on 363 cases could be used. For purposes of comparison the histories of 349 males were studied. Table 16 shows the figures obtained.

TABLE 16

Hfi	Cases	Character of the Disturbance					
		Diabetes A	Glycosuria B	Hyperglycæmia without Report of Glycosuria C	Total	Percentage A+B+C	Percentage A+B
Females with	233	20	11	10	41	17 6	13 3
Females without	363	24	26	17	67	18 5	13 8
Males without	349	26	29	15	70	20 0	15 8

It is difficult to decide how far it is permissible to draw definite conclusions from this table. It indicates, however, that the incidence of major disorders of the carbohydrate metabolism in females does not seem to be greater in women affected with Hfi than in those not presenting it, and that they seem to occur more frequently in the present series of males than in that of the females reported. Theoretically, the coexistence of Hfi and glycosuria or Hfi and diabetes is nevertheless interesting.

The possible relationship between disorders of the carbohydrate metabolism and the thickness of the parietal bones was also made the subject of a preliminary investigation, though only on a comparatively limited number of skulls—amounting in all to forty. Although the figures obtained do not permit definite conclusions, we considered them nevertheless worthy of publication (Table 17).

The above statements suggest that *both hypertension and hypertrophy of the heart seem to be common in women manifesting MS and that they probably play a significant part.*

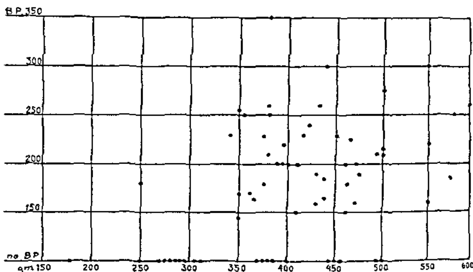


DIAGRAM 12

Distribution of the cases with Hfi in regard to blood pressure (to the left) and heart weight (below). Cases without blood-pressure data at the base line.

3. Disorders of the Carbohydrate Metabolism—It is well known that disorders of the carbohydrate metabolism are common in obese and elderly women It has also long been known that the coexistence of excessive growth of hair on the face and glycosuria is fairly common in obese women. The term used by French authors, "la diabète des femmes à barbes," is likewise well known. Since disorders of the carbohydrate metabolism due to diabetes coexist with acromegaly in a large number of cases, and hyperglycæmia and glycosuria may occasionally coexist with CS, it is hardly surprising that metabolic disorders of this type may be associated with MS. In the monograph of 1937 by the present author, which is in the main based on the cases classed in Group III, attention was directed to the coexistence of MS and diabetes: "In a fairly large number of cases there was diabetes mellitus; its frequency, however, was roughly the same as in the cases not presenting Hfi"

In the attempt to give a clearer picture of these conditions the correlation between Hfi, abnormal growth of hair on the face and adiposity on the one hand, and on the other, disorders of the carbohydrate metabolism, was determined on the basis firstly of the histories of 700 cases of Group V, and secondly on those of the male patients recorded at the same time (Tables 16 and 20). It was, unfortunately,

not possible to study the minor disorders of carbohydrate metabolism in the majority of the cases because the relevant data were incomplete. The instances in which the blood-sugar content was less than 110 to 115 mg. per cent. and the urine negative for sugar (Almén and Benedict) were therefore considered negative cases, and those in which the urine was positive for sugar and the blood sugar elevated as well as the cases merely referred to as cases of diabetes in the histories, were classed as positive cases. Although we are fully aware that this classification implies a comparatively great simplification and generalization, we feel that it nevertheless helped to shed some light on the frequency of the coexistence of disorders of the carbohydrate metabolism and MS.

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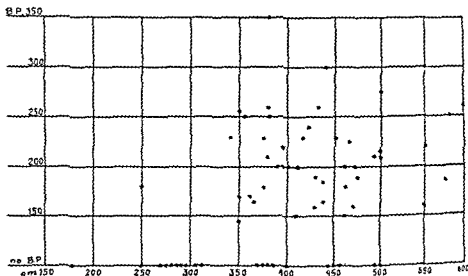


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Hfi	Cases	Character of the Disturbance					
		Diabetes A	Glycosuria B	Hyperglycæmia without Report of Glycosuria C	Total	Percentage A+B+C	A+B
Females with	233	20	11	10	41	17 6	13 3
Females without	363	24	26	17	67	18 5	13 8
Males without	349	26	29	15	70	20·0	15 8

It is difficult to decide how far it is permissible to draw definite conclusions from this table It indicates, however, that the incidence of major disorders of the carbohydrate metabolism in females does not seem to be greater in women affected with Hfi than in those not presenting it, and that they seem to occur more frequently in the present series of males than in that of the females reported Theoretically, the coexistence of Hfi and glycosuria or Hfi and diabetes is nevertheless interesting.

The possible relationship between disorders of the carbohydrate metabolism and the thickness of the parietal bones was also made the subject of a preliminary investigation, though only on a comparatively limited number of skulls—amounting in all to forty. Although the figures obtained do not permit definite conclusions, we considered them nevertheless worthy of publication (Table 17).

TABLE 17

Hyperglycæmia Glycosuria Diabetes	Parietal Bones				Total
	Thin	Rather Thin	Rather Thick	Thick	
No disturbance .	4	10	8	3	25
Disturbance . .	0	2	4	1	7
No data . .	4	1	1	2	8
Total .	8	13	13	6	40

It seems clear that a positive correlation between these conditions does not exist.

It is [illegible] the frequency of the sc[illegible] of the [illegible] investigations will be necessary before the percentage of distribution of the so-called hypophyseal form of diabetes in the sexes can be definitely determined and before the question whether the presence of Hfi indicates its coexistence can be clarified. Considering the structural and functional differences frequently existing between the hypophysis of a man and that of an old woman, a difference in the percentage of distribution in the sexes might exist. The hypophysis of an old woman possibly may be more "susceptible" than that of a man

The correlation between abnormal growth of hair on the face and disorders of the carbohydrate metabolism was investigated in a similar manner.

TABLE 18

Hairiness of the Face	Total Number	No Disturbance	Hyperglycæmia	Glycosuria	Diabetes	Percentage
Normal .	254	204	15	22	13	19 7
Increased .	208	163	9	15	21	21 6 } 20 0
Pronounced .	87	70	4	3	10 }	17 5 }
Very pronounced	39	34	1	1	3 }	

Table 18 does not indicate any considerable differences Expressed in terms of percentage the incidence of the disorders in the presence of

normal hairiness of the face is roughly the same as that in cases showing abnormal facial growth of hair. It is rather surprising that the frequency of disorders of the carbohydrate metabolism is not higher in females presenting abundant or excessive growth of hair on the face than in those showing normal hairiness on the face Nevertheless the coexistence of glycosuria or diabetes and abnormal growth of hair on the face, " la diabète des femmes à barbes," is a striking and interesting endocrine syndrome occurring fairly often.

Finally, the cases in which there was *coexistence of adiposity and disorders of the carbohydrate metabolism were compiled and compared.*

TABLE 19

Nutritional State	Total Number	No Disturbance	Hyperglycæmia (A)	Glycosuria (B)	Diabetes (C)	Percentage	
						A + B + C	B + C
Very thin and thin	83	71	2	5	5	14·4	12 0
Poor	41	39	0	0	2	5 0	5 0
Normal .	148	115	9	11	13	22 3	16 2
Fat .	147	117	6	15	9	20 4	16 3
Very fat	116	97	7	7	15 }	23 0	17·4
Obese .	45	37	2	2	4 }		

As was mentioned above, it was often extremely difficult reliably to assess and record the nutritional state of the patients because subjective factors were operative. This also explains the frequently rather vague distinction between the cases classed " moderate " and " abundant " and those grouped " fat " and " very fat." Although the number of the series classed " poor " is very limited, it is interesting that this group contains only 2 cases of disorders of the carbohydrate metabolism The high figures obtained in the groups " fat " and " very fat " are also worthy of attention

4. Neurological and Psychiatric Symptomatology—Some of the cases of Group V—which numbered in all 108 instances—came from the psychiatric clinic of St Erik's Hospital. In 44 (40 per cent.) Hfi was present and in 64 (60 per cent.) it was absent The average age of the cases presenting Hfi was 69 6 years, and that of the instances in which it was absent 67·5 years. These figures do not indicate *any difference between the cases coming from the psychiatric clinic and those coming from the medical and surgical clinics*

Of the females presenting mental disorders, 13 were afflicted with severe extreme Hfi. The psychiatric diagnosis varied. There was one case of dementia paralytica and one of idiotism ; in the majority of the cases senile dementia was present.

Milder forms of psychiatric disorders of senile character were fairly common in the females coming from the medical and surgical clinics Evidently they were masked by the severe somatic manifestations. There was no marked difference between the females affected with Hfi and those in which it was absent. It should here be recalled that brain-weight and the presence of cerebral atrophy correspond exactly in the cases presenting Hfi to those not presenting it (p. 75).

Of the 29 cases manifesting very severe Hfi (*i.e*, + + +) 5 at least showed a marked flattening of the frontal lobe. In some instances it was less marked, probably because of the coexistence of other alterations of the brain, viz., softening and hæmorrhages.

Of the 76 cases of Hfi + + or Hfi + + + which were subjected to a careful clinical examination, as many as 50—*i.e.*, two-thirds of the patients—showed lesions of the brain which were recognizable even on macroscopical examination and coexisted with more or less strongly pronounced neurological and psychiatric symptoms. Softening of the brain was the predominant organic alteration; in as many as 36 there were foci of softening of long standing (15 cases), or of recent standing (12 cases), or both coexisted (9 cases), which explain the neurologic and psychiatric symptoms that had persisted for years Cerebral hæmorrhages were found in 7 cases; in 3 of these they were of older standing. On post-mortem examination a subdural hæmatoma of long standing was found in 2 cases, a tumour of the brain in 4 and sclerosis disseminata in 1. Macroscopically, the brain was found to be almost normal in 12 cases.

A variety of subjective symptoms—viz., headache, vertigo and so forth—played a comparatively important part in many cases. They could in the main have been caused by hypertension or valvular disease recognized at autopsy.

At this point it should be mentioned that Hfi was in no instance the principal disease—that is, the disease for which the patient sought medical advice In 76 cases of severe Hfi the anatomical and clinical examination revealed the coexistence of a principal disease and a cause of death which frequently bore no relation to MS. On the other hand a glance at the report of the cases will suffice to bring out the importance of hypertension and its implications. The close relationship between hypertension and MS has been emphasized before in this book. Adiposity played a crucial part in a fairly large number of cases (see report of the cases).

When attempting to go a step further in the clarification of the problems connected with MS it is possible to proceed in two different ways—*i.e.*, either by selecting suitable living examples of this condition and controlling them until they go to autopsy or by commencing investigations on autopsy cases and then going back to the study of clinical manifestations. Notwithstanding the great advantages of the

latter method, it has one disadvantage of great weight inasmuch as some of the minor clinical symptoms—perhaps even the most essential ones which are considered to be characteristic of MS and Hfi—might have been masked and overshadowed by the symptoms of the principal disease during the lifetime of the patient and therefore escaped attention. ROSSIER and SECRETAN seem to have recognized this, and therefore included in their report of cases only the purely clinical ones which came under their own observation and refrained from publishing those which had been put at their disposal from other quarters. They stated · " Les examens orientés dans d'autres directions nous donnent peu de renseignements intéressants."

Despite the disadvantage remarked upon above, the last-mentioned method has been chosen, and the 700 cases reported in the present paper were investigated by a study of the post-mortem findings, special consideration being given to the 76 cases of particularly severe Hfi

B. MALES

The entire series which came under observation comprised only 9 males This figure by itself is evidence that MS is extremely rare in men The post-mortem examination in conjunction with the investigations on Hfi was made on only four instances. On these grounds the relative frequency of Hfi in both sexes could approximately be determined. In a series of 1,000 autopsy cases of females, 390 cases of Hfi were recognized. Of approximately 1,000 cases of males on which a post-mortem was made, 4 were cases of Hfi Thus the relative frequency of Hfi in women and men was in the ratio of 100 to 1 in the present material

When tabulating the 9 male cases mentioned, the results given in Table 20 (p. 86) were obtained.

Table 20 shows that the series of cases examined comprised men between the ages of 53 and 75 Three were tall (178 to 181 cm.), some were of the pyknic type and some were " stocky " In Case 4 there was acromegaloidism. Cases 2 and 3 suggested the presence of CS. The degree of severity was assessed + in 5 cases : in Cases 1 and 7 it was classed + +, and in Cases 2 and 9 it was considered + + +. The condition of the growth of hair was mentioned in 3 cases only. In 2 (Cases 2 and 3) it was of the type seen in old women. These 2 cases also showed pronounced adiposity of the feminine type. Case 1 was also very fat Case 7 was fairly fat, and the nutritional state of Cases 4, 5, 6, 8 and 9 was either fairly good or poor The condition of the testes was particularly interesting, but only 6 cases were microscopically examined In 5 of them atrophy and sclerosis of the genital gland of more or less pronounced degree were present. The cause of

TABLE 20

Cases	Age	Height	Constitution	Hfi	Hairiness	Nutritional State	Genital Organs	Heart	Liver and Pancreas	Skeleton	Hypophysis	Principal Disease; Cause of Death
1	53	169 cm	Pyknic	+ +	·	Very obese	Atrophy and sclerosis of testes, 20 g	620 g.	Atrophy, lipomatosis	..	Macroscopically normal	Hypertension, diabetes, cerebral hæmorrhage
2	56	170 cm.	Pyknic	+ + +	Poor on the face and pubic region, hairless axillæ	Extremely fat, also on the hips, 145 kg	Atrophy and sclerosis of testes (25 g.) and penis	515 g.	Cirrhosis and lipomatosis of liver and pancreas	Normal	Large cyst; atrophy	Adiposity, cirrhosis of the liver
3	62	·	Pyknic, slender extremities	+	Everywhere poor, pubes of female type	Very fat, marked mammæ and hips	Testes macroscopically normal, atrophy of penis	Hypertrophy	...	·	Augmentation of Ac's and Bc's	Arteriosclerosis, softening of the brain
4	62	181 cm	Stout, acromegaloid	+		Fat, but thinner than before	Atrophy and sclerosis of testes, 16 g	500 g	Slight cirrhosis of the liver	Slight osteoporosis	Slightly enlarged	Carcinoma of the stomach
5	65	Medium	Rather stout	+	·	Normal, but thinner than before	Atrophy and sclerosis of testes (?)	Hypertrophy	Cirrhosis and carcinoma of the liver	Metastatic tumours	..	Cirrhosis of the liver
6	65	173 cm	Ordinary	+	Normal	Slightly emaciated	Testes normal, 40 g	400 g	Congestion	Normal	Macroscopically normal	Carcinoma of the stomach
7	68	179 cm.	·	+ +		Fat	Testes normal, 40 g	430 g	Hyperglycæmia	Metastatic tumours	Macroscopically normal	Carcinoma of the sigmoid flexure
8	73	178 cm	Ordinary	+	Normal	Scanty	Atrophy and sclerosis of testes, 13 g	380 g.	Cirrhosis of the liver	Osteoporosis, spondylosis	..	Cholecystitis with abscess
9	75	Medium	Ordinary	+ + +	·	Good	Atrophy and sclerosis of testes	745 g.	Normal	Spondylosis	...	Heart disease

these alterations has not been definitely established. In this connection it is interesting that 4 of the cases presented cirrhosis of the liver; in an additional case there was coexistence of Hfi. The coexistence of cirrhosis of the liver and alterations of the testes has been a common finding on post-mortem examinations made at St Erik's Hospital in recent years (HENSCHEN, 1931), and the frequency of its occurrence has been frequently reattested. The hypophysis has not been sufficiently carefully examined in these cases and therefore does not permit any definite conclusions. The large cyst, however, found in Case 2 is particularly interesting. In 7 cases there was—though no valvular diseases were demonstrable—hypertrophy of the heart (in 3 cases it weighed between 500 and 620 g), suggesting the coexistence of hypertension, although it was clinically recognized in a few cases only. Case 1 was a diabetic and in Cases 2 and 7 there was hyperglycæmia.

CHAPTER FIVE

GENERAL DISCUSSION

A. MORPHOLOGY AND MORPHOGENESIS

THE extensive literature on Hfi and MS, which is now available in the form of case notes, articles, dissertations and monographs, allows a general survey and thorough discussion of many problems connected with the anatomy, radiology, clinical features and pathogenesis of the syndrome.

According to descriptions, which, of course, cannot be quite exact, there have been to date more than 1,000 cases of Hfi in women and about 40 cases in men published by other authors. The majority have been exclusively clinical studies. To these are added the author's own autopsy material comprising 390 female and 9 male cases, which are discussed in his own publications.

A certain weakness of the literature, mainly of recent date, is the comparatively small number of autopsy cases. Entirely clinical statements predominate, in which all exact information as to the presence of Hfi and also particularly on the behaviour of the brain is lacking. *In cases of early and slight, often radiologically doubtful, Hfi, and especially in elderly individuals with psychical and neurological symptoms, the autopsy forms the sole real foundation of discussion. Experience shows that these symptoms very often depend on organic alterations of the brain.* For these reasons decisive significance must be accorded to autopsy findings in the following discussion.

The basis of discussion of the different aspects of the present syndrome is an exact diagnosis and an accurate recognition of the pathogenesis of Hfi and of other forms of hyperostosis of the skull.

Morphology and Morphogenesis

MORGAGNI having given the first description of Hfi, it was a very long time until it was once more described by a pathologist. In the nineteenth century ROKITANSKY seems to have been the first to be interested in Hfi. His words are worth quoting: "On the tabula interna a form of protuberance occurs next to the crista frontalis in the shape of stretched or twisted rolls" This kind of exostosis coincides "very frequently with sclerosis of the affected and other bones of the skull, and not infrequently with ossification of the dura mater." The periosteum is said to be "in most cases of normal character above the exostoses, but sometimes thicker, hypertrophied and more closely adherent." *The Hfi is, according to ROKITANSKY, like* "an osseous

substance poured over the bone and congealed—sometimes masses of osseous substance are formed, which seem to have been poured on in small drops and congealed on the bone. Sometimes these masses may have a smooth surface, sometimes it is as though streams of congealed osseous substance had been poured over larger osseous plains." The Hfi is, as he quotes on another occasion, "the result of an increased bone formation (nutrition of the bone) due to unknown conditions and generally develops slowly, mostly in the later stages of life." It seems to be the opinion of ROKITANSKY that these osseous aggregates are products of the dura mater.

Then follows a series of shorter descriptions, among which particular stress should be laid on those by VIRCHOW and ENGEL; thereafter it has been referred to in the survey of the literature.

Explicit and well executed is the one which NAITO published in 1924 (German text):—

"The senile cranial hyperostosis represents a peculiar form of thickening of the skull, which is characterized by flattish osseous aggregates at the inner surface of the anterior parts of the skull, mostly only of the os frontale on both sides The form and size of the skulls shows no abnormality, even the average thickness generally does not exceed normal limits. The structure of the skull is of normal character, the sutures and the furrows of vessels show no deviation from the normal condition. On the other hand, the frontal bone shows a considerable thickening, in the form of flattish osseous aggregates In typical cases they consist of spongy tissue and are covered by a thin layer of compact bone. The parts of the frontal bone nearest the median line, as well as the orbital parts, are mostly free from hyperostosis Posteriorly the hyperostoses generally do not exceed the limit of the frontal bone, but occasionally a prolongation extends to the neighbouring parts of the parietal bone In these cases the zone, corresponding to the coronal suture, remains as a furrow between the frontal and parietal accretions The accretions of bone show, on the interior surface, a fissuring like a range of mountains. The transition to normal bone is seldom gradual but generally sharply demarcated The base of the skull as well as the facial part show no alterations."

To DRESSLER (1927) we owe a very good and explicit description He discusses two skulls: one of a man 68 years old, rather heavy and generally thickened, and a lighter one, with marked atrophy of the rest of the calvaria, in a woman. Both these cases are interesting if only for the reason that they demonstrate the independence of the Hfi from the bony state of the rest of the skull. DRESSLER was the first to perform a thorough microscopical examination of Hfi. He distinguishes two main forms a spongy, which is more frequent, and a less frequent compact form. In the spongy form the diploe occupies nearly the whole cross-section; on the interior surface generally only a narrow strip of newly formed bone is found. In the compact form the diploe appears only as a narrow strip, whilst the tabula interna remains as a fairly deep compact strip of bone Besides these

fundamental forms, intermediate forms and variations are found. Common to all forms, according to DRESSLER, is an irregular thickening of the entire bone on the inner surface together with a smooth exterior surface regularly showing signs of resorption.

On the nodular interior surface he finds a somewhat variable appearance. *On all the prominences of the inner surface there are to* be observed layers of accretion of very variable width. Strata of lamellar arrangement with putty lines can be distinctly made out. Often two or three such systems of accretion *with putty lines are found lying* one above the other. This is especially the case in the compact form of Hfi. In the spongy form the superimposed lamellæ are transformed quickly into spongy osseous tissue. The Volkmann perforating canals which form the communication between the vessels of the dura and the marrow space are also present in the new tissue. Even at the exterior surface of the frontal bone now and then traces of bony accretion are found.

DRESSLER has also examined *the histogenesis of Hfi* and has observed, among other things, the transformation of the dura mater into osseous substance. In no case could he describe real osteoblasts. All slides offered practically the same appearance of a direct transformation of the dural connective tissue into osseous tissue. The nuclei of the dura become bone nuclei, and the fibres osseous lamellæ by direct hyalinization. If the ossification, as sometimes happens, predominantly occurs in the middle stratum of the dura, fibres of normal dura may be enclosed in the bone tissue. DRESSLER has never seen changes *of inflammatory type. These accurate examinations, which were* performed in the institute of SCHMORL, are of great importance.

A good description and excellent macroscopical illustrations are found in GREIG's article, though he does not seem to have performed microscopical examinations. Writing about the morphogenesis of the Hfi, he differs from DRESSLER's descriptions as well as from our own, and therefore deserves to be referred to here : "The osteophytes have the appearance of having grown from the bone, of having spread out with the dura mater and not of having developed in connection with the membrane and become secondarily fused to the endocranial surface. The features are those of excrescence rather than of accretion, and the name osteophyte . . adequately suggests this quality. The growth is not associated with intradural ossification or calcification unless fortuitously. . . . "

STEWART (1928) was also interested in the morphology of Hfi. *He* distinguishes three types : (1) Two thick tabulæ with normal diploe ; (2) thickened, bulbous or flat tabula interna ; (3) increased diploe between two thin tabulæ.

The examinations of MOREL (1930) include both the macroscopical and microscopical behaviour of Hfi. The prominences on the internal

surface are "sometimes extremely rich in osteoblasts," which stands in sharp contrast to DRESSLER's findings. The laying down of bone seems to be very active in that area. Signs of inflammation are lacking. In one case the tabula interna does not possess the general eburnated appearance, but, instead, the diploe reaches almost directly to the dura. The inner surface is here extremely irregular, and at the prominences of the bone the dura is hardly visible, being incorporated in the bony tissue.

In a paper on senile hyperostosis of the roof of the skull ERDHEIM (1935) discusses Hfi, which he obviously considers to be only a special morphological form of "senile" change He does not state that Hfi appears almost only in women, and DRESSLER's work is not mentioned. The histogenesis of Hfi is described shortly and clearly; the results coincide with those of DRESSLER, the similarity with the bone formation which is spread over nearly the whole of the inner surface of the senile skull being clearly recognized. It may be noted here as an important detail that ERDHEIM is acquainted with the smaller protuberances which sometimes occur at the os parietale and occipitale, and which he describes.

In our own publications (1935-45) the general morphology of Hfi was not described very thoroughly, so many excellent descriptions being already available. Meanwhile it will be emphasized as our own opinion "that Hfi develops independently of the other skull changes. Hfi occurs equally in heavy and light, thick and thin, sclerotic and porous skulls." Hyperostoses of the highest degree were described in skulls of ordinary thickness and weight, while on the other hand we observed numerous cases of Hfi combined with intense general thickening and sclerosis of the skull.

In the years 1935-36 the important examinations of MOORE were published, establishing and defining his now well-known and generally acknowledged four types of hyperostosis. The relations of the different types to each other will be entered into more closely in the discussion on the pathogenesis, so that it need only be emphasized that according to MOORE the Hfi is combined with a more or less explicit general thickening of the skull, as the following table from one of his works shows :—

	Frontal		Parietal	
	R.	L.	R	L.
Average Thickness (in Millimetres)—				
Normal (582 specimens)	4	4 25	3	3 25
Hfi (29 specimens)	6	7	4	4
Variations in Thickness (Millimetres)—				
Extreme	19	20	11	11
Minimum	3	4	3	4

The fact that Hfi is very often combined with other forms of hyperostosis leads him to the conclusion that all these types, including even Hfi, have "the same fundamental etiology." We shall refer to these questions more fully later on.

Several scientists, namely CARR, MONIZ, ROSSIER, SECRETAN and OLDBERG, concurred in the opinion of MOORE, mainly on the basis of radiological observations. ROSSIER and SECRETAN not only saw an association of Hfi with Hcd, but even had the impression "that the different forms may pass over into each other." The greater part of their cases, however, were typical Hfi. According to OLDBERG, "hyperostosis frontalis interna is positively correlated with a diffuse *thickening of the parietal bone* and consequently *with the diffuse* thickening of the calvaria"

Anatomical Diagnosis of the Hyperostosis

Morphologically, frontal hyperostosis is very characteristic and in typical cases easy to recognize in terms of the above descriptions by various authors. Until we are in a position to survey all etiological factors we must forgo discussing *whether or not we are here dealing with a uniform change of constant pathogenesis.*

Diagnostic difficulties are especially frequent in cases of early hyperostosis and, in addition, atypical types are sometimes difficult to recognize. Differentiation of frontal hyperostosis from other forms of hyperostosis of the skull is nearly always easy.

The first category, including the early and quite slight hyperostosis, is hardly mentioned in the literature based on autopsies. Only NIEUWENHUIJSE indicates in a lecture that he includes cases with early *alterations.*

In our own material, and especially in Groups III and V, the cases with slight or commencing changes form a very large part. In Group III they form about 25 per cent, in Group V about 23 per cent., of the positive cases. To begin with, it is impossible to decide to what extent the cases marked with a ? belong to the slight or early stage of the hyperostosis, *as in these cases diagnosis is achieved only* after a thorough and critical examination of many cases. Diagnostically, in our experience, the impressions on the inner surface of the skull produced by the brain gyri must first be taken into account, as they are not seldom very well marked on the frontal bone. Where the dura is adherent to these impressions, the relief may be rather similar to a slight frontal hyperostosis. However it must be noted that the impressions of the gyri on the inner surface of the skull are composed only of concavities, while the outline of the frontal hyperostosis is predominantly one of convexities; there is often the impression, even with quite slight hyperostosis, that there has been an aggregation of

newly formed bony substances on the tabula interna, such as ROKITANSKY and ERDHEIM very strikingly compare with wax poured out in layers.

As has been already mentioned, diagnostic difficulties occur occasionally because of an atypical appearance of the hyperostosis. *However, in our experience to date, the other forms of hyperostosis of the skull offer so few similarities to the real hyperostosis frontalis interna that mistakes can hardly occur, at least at autopsy.*

It is questionable if they can be separated radiologically. In every case OLDBERG, basing his opinion on radiological examinations, reckons with "all transitions between slight, diffuse thickenings and others of a more predominant and defined character." Therefore he denies the possibility of a differential diagnosis of Hfi from Hcd and Hfp. In opposition to this view MOORE has already declared in 1936 that Hfi is "morphologically distinct."

Confusion with the *puerperal osteophyte*, which earlier we had thought impossible, may occur in certain conditions. As examples, some of DRESSLER's cases and the case recorded on page 40 may be mentioned. Only the microscopical examination disclosed in our case the possibility that there may have been the question of a slight puerperal osteophyte in a skull combined with early Hfi.

Hfi may show great similarity with the skull changes in acromegaly, especially in the small warty form, and in general the impression is gained *that here we are dealing with closely similar changes*, which in Hfi are more limited to the anterior part and more coarsely knobby and furrowed, compared with acromegaly where they are more dispersed and tuberculated We refer to Fig 6.

The Microscopical Aspect of Hfi

There is not much to add to the microscopical examinations of DRESSLER and ERDHEIM on the behaviour of the skull in Hfi. Our own experiences confirm the existence of the processes found by them. Only in a single case did there exist besides the typical appearance of lamellæ and putty lines lying close to each other a change of another form, which looked like the puerperal osteophyte (Fig. 52).

According to Dressler's, Erdheim's and our own examinations, in Hfi the process appears to be one of an irregular laying down of osseous lamellæ, which are derived from the exterior and median layers of the dura. In effect it is of the [illegible]

Therefore we cannot agree with the opinion of GREIG that we are here dealing with real "excrescences." Likewise, we were not

able to ascertain the abundance of osteoblasts recorded by MOREL, although, like ERDHEIM, we observed these elements in small numbers.

So that Hfi is the result of an irregular, sometimes extraordinarily strong ossificating activity of the dura, continuing over many years and being in some degree typified in the diffuse bone formation over the inner surface of the skull, especially in elderly women.

The Dura

As first MORGAGNI and later many other authors have emphasized, the dura in Hfi generally is more or less closely fused with the roof of the skull, particularly at the anterior part. Exceptions to this are rare, but we have seen in a few cases of undoubted Hfi with chronically increased intracranial pressure (tumour of the brain) and erosion of the tabula interna, a quite loosely attached dura even at the anterior part above the hyperostosis, this also having been observed by other authors

Calcification and ossification of the falx and tentorium occasionally occur in Hfi and are mentioned by some authors · GREIG, MOREL, MOORE, DONINI, and KNIES and LE FEVER, among others. In some cases we ourselves saw such calcifications. It is not known if these alterations occur more frequently in Hfi than in a normal series. Our own experience does not favour this view.

General Skeletal System

The few statements on the skeleton in cases of Hfi which are to be found in the literature, are rather contradictory. MOORE has the impression that the other bones only showed alterations due to age, and that " they in no wise differed from like changes found in those skeletons considered normal " Therefore it is of interest that OLDBERG recently could state that " in cases of Hfi as well as of acromegaly an enlargement of the sagittal diameter of the atlas radiologically " existed

Our own material showed variable appearances. In some cases a strikingly robust, coarse, even sclerotic skeleton was observed. *In numerous cases a pronounced osteoporosis was present.* Our calculations decidedly support the fact that osteoporosis is to be found more frequently in Hfi-positive than in Hfi-negative cases ; likewise, that a spondylosis deformans occurs more frequently in Hfi than normally. *The great frequency of osteoporosis in Hfi recalls the osteoporosis in CS.* The increase in frequency of spondylosis deformans in Hfi may possibly

be connected with the fact that these individuals often are heavier and more robust than those without Hfi. Exact figures are to be found on page 64.

Radiological Examination of Hfi

NAITO and SCHULLER were the first to examine Hfi radiologically (1923). In the monograph of NAITO, 10 apparently typical cases are described. CASATI published further examinations in 1926 and 1936. The lecture of HELLMER on the radiology of Hfi is important, in that for the first time he stated the great frequency of Hfi and the absence of positive clinical symptoms. Instructive X-rays were published even by MOREL. After this time papers on radiologically diagnosed cases became more and more numerous

The most important studies are those of MOORE (1935-36). He considers the possibility of determining Hfi by X-ray examination very high. "The surest means of determining the existence of the hyperostosis is by radiographic examination. Certain degrees of types of hyperostosis may readily escape notice at autopsy." If MOORE with the term "hyperostosis" intends to signify all kinds of cranial hyperostosis, one may be completely in accordance with him; particularly is this the case with MOORE's nebula frontalis, which appears best in the X-ray. Anatomically the nebula can be recognized by a minute examination of the diploe, both tabulæ being unchanged here. Even Hfp may be recognized only occasionally by the reports on sections, although it can be determined without difficulty in palpating the roof of the skull. But if the case is an Hfi, the autopsy diagnosis seems to be superior to the radiological method in our own opinion if, as so often happens, it is a question of a quite slight or commencing case.

The question how far a radiological diagnosis in quite early and slight cases may be possible can hardly yet be answered, comparative anatomico-radiological examinations scarcely being available

Until now our own comparative examinations include only a limited number of skulls. The greater part of these X-rays were taken from the lateral aspect. They were made by Dr K LINDBLOM, Lecturer in Radiology at the Caroline Institute and an expert in X-ray examination of skulls The exposure was the same as would be given to a living person. In this place we beg Dr LINDBLOM to accept our thanks for the X-rays and for much good advice

The examinations were limited to the very slight changes, anatomically just positive, and to the borderline cases. Skulls without Hfi were taken as control. The radiological verdict was given by Dr LINDBLOM without preceding knowledge of the autopsy appearance of the skull.

In 9 cases without macroscopical Hfi, among them 4 with Hfp, even the X-ray examination was negative in regard to Hfi. In 3 cases

with Hfi(?) added together with other forms of hyperostosis, the X-ray examination showed the following result :—

TABLE 21

Case	Anatomically	X-Ray
1	Hfi (?)	Hfi (?)
2	Hfi (?), Hfp	Hfi –
3	Hfi (?), Hcd, Hfp	Atypical Hfi

In 9 cases with Hfi(+) the X-ray examination proved to be as follows :—

TABLE 22

Case	Anatomically	X-Ray
1	Hfi(+)	Hfi(+)
2	Hfi(+)	Hfi(+)
3	Hfi(+)	Hfi +
4	Hfi(+), Hcd	Hfi –
5	Hfi(+), Hcd	Hfi (?)
6	Hfi(+), Hfp	Hfi(+)
7	Hfi(+), Hfp	Hfi(+)
8	Hfi(+), Hfp	Hfi +
9	Hfi(+), Hfp	Hfi +

Nine cases with Hfi + showed the following results on X-ray examination :—

TABLE 23

Case	Anatomically	X-Ray
1	Hfi +	Hfi (?)
2	Hfi +	Hfi(+)
3	Hfi +	Hfi +
4	Hfi +	Hfi +
5	Hfi +	Hfi +
6	Hfi +, very thin	Hfi +
7	Hfi +, Hcd	Hfi(+)
8	Hfi +, Hcd	Hfi +
9	Hfi +, Hcd	Hfi +

The comparative examination of the anatomy and radiology of thirty skulls thus showed *a very close correspondence by both methods*, the series being given to a radiologist skilled in this branch. In none of the Hfi-negative cases did the X-ray diagnosis become Hfi-positive.

Only in 2 cases of Hfi(+) in connection with Hcd the X-ray examination proved to be negative or doubtful. In 3 cases of Hfi(+) the Hfi was somewhat overestimated; in 2 of these cases a Hfp coexisted with Hfi(+), which may have contributed to the somewhat high valuation of the Hfi Among the cases of Hfi+ the X-ray diagnosis was doubtful in 1 case, and in 2 cases Hfi was underestimated.

In spite of the very close agreement of the two methods we must allow greater exactitude to the exclusively anatomical diagnosis. However, MOORE's nebula frontalis, which morphologically can only be diagnosed with the aid of microscopical examination, forms an exception, and therefore the X-ray examination seems here to be superior to the macroanatomical.

B. FREQUENCY OF THE HFI: AGE

As in many other pathological conditions, it is very difficult to get a fairly exact conception of the occurrence and frequency of Hfi. It is generally emphasized that this change is found principally in women, but the statements on the relative frequency in men and women are highly variable.

Much depends upon whether—as the present author has done—the cases of quite slight and early Hfi are included; if so, the number of cases increases considerably. Radiologically these smallest alterations often are either doubtful or invisible, so that for these X-ray diagnosis is of doubtful value. Therefore if the real frequency of Hfi is to be stated, only a large, uniformly collected post-mortem series is of value. Hfi occurring especially after the climacteric, the figures of frequency are strongly influenced by subdivision of the cases into age periods by decades The younger the women, the lower the percentage. Every decade has its own number of frequency. Such things as race and average constitutional build have probably a certain importance, Hfi being, it seems, the expression of a constitutional factor.

Frequency in Women

Most of the authors who have written about the frequency of Hfi have expressed themselves in general and subjective terms: "rather frequent" (HELLMER, 1928), "a rather rare condition" (STEWART, 1928), "a rare disease" (FRACASSI and MARELLI, 1936); "unusual clinical finding" (JAMES, 1936), "It is not a mere chance that the Hfi is met particularly in asylums for mental diseases and in neuropsychiatrical hospitals, it being apparently more frequent there than anywhere else" (MOREL, 1937), "in senility, particularly in women, frequently occurring thickening" (SCHMIDT, 1937); "it is a rare disease, which is found especially in asylums for the insane" (MONIZ, 1938); "by no means rare" (PENDE, 1940); "rare disease, but certainly

more frequent than generally supposed" (KIAER, 1941); "more frequent than generally supposed" (ANDERSEN, 1942).

Attempts to assess the frequency by radiological examinations have been very variable: In 1936 MOORE found 96 cases of Hfi among 6,650 skulls (1·4 per cent.); RICHTER, who examined 1,227 skulls in 1939, found in spite of the small series nearly the same number—93 positive cases (no less than 7·6 per cent.); ELDRIDGE and HOLM (1940) found 50 positive cases among 200 women (thus 25 per cent.), among them 28 per cent. before and 72 per cent. after the fortieth year of age; JACOBSON and NIELSEN (1942) saw 2 cases among 100 unselected women, LOUW (1943) found Hfi only in 0·5 per cent. of the 10,000 cases whose roentgenograms he was able to study. OLDBERG, with good reason, lays stress upon the difficulty of distinguishing radiologically an increased thickening of the frontal bone from Hfi, found in a "normal material" of 323 women with an equal distribution of all age periods, a frequency of 4·3 per cent. According to GROLLMAN and ROUSSEAU metabolic craniopathy is a syndrome "of relatively frequent occurrence," being found in approximately 1 per cent. of "a general hospital population"

Even the exclusively anatomical examinations of Hfi give quite variable figures, this partly being connected with the fact that most authors have taken into consideration only very obvious cases, partly because the material has included male skulls in varying numbers. BULLEN found only 1 per cent. Hfi among 1,565 autopsies from an asylum, FREEMAN, 24 cases of Hfi (1·5 per cent.) among 1,514 autopsies. The large survey of DRESSLER, including 1,632 autopsies in Dresden, resulted in 71 cases of Hfi (4·4 per cent); MOORE found 24 cases (3 6 per cent) among 660 skulls from the Anatomical Institute of the Washington University in St Louis Nearly double frequency was found by CANAVAN, who was able to find 230 cases among 3,250 autopsies (7·1 per cent) GREIG's figures are much higher He examined 168 skulls from a museum and found Hfi in 32 cases (17 per cent.). Particularly high are our own figures, which include quite slight and early cases Among the 200 unselected women between 31 and 95 years of age, which our Group III includes, 66 (33 per cent) showed Hfi, *among the women over 50 years no less than 40 per cent. were affected with Hfi* Somewhat higher was the frequency in Group V, including 700 women between 25 and 95 years of age Here 266 cases (38 per cent.) showed Hfi. Within some five-year periods the number amounted to over 50 per cent Meanwhile it may be emphasized here that this large group does not form an unbroken series, but, as detailed more closely above, represents material, preserved for certain aims, thus undoubtedly increasing somewhat the figures obtained.

Connected with the above discussion MOREL and CANAVAN, among others, state that the frequency of Hfi should be greater in psychiatrical

material than in patients from other clinics. MOREL is even of the opinion that it should occur especially in hospitals for mental diseases and in neuropsychiatrical clinics. MONIZ is of the same opinion. *It is not easy to understand why Hfi really should be increasingly frequent in psychiatrical material, for these patients are in every way so variable in somatic respect and, besides, belong to so many heterogeneous forms of psychoses.*

In our own series of 700 cases, 110 cases were derived from the psychiatric clinic. The distribution of the cases is to be seen in the table :—

TABLE 24

Distribution				Positive	Negative	Doubtful	Total
(+)	+	+ +	+ + +				
13	19	9	3	44	63	3	110

Among the insane the frequency of Hfi was thus 40 per cent., which, in regard to their advanced age in comparison to the other material, represents rather a low number. *Estimating the frequency of Hfi, the basis must be unselected clinical material, which is not the case in either* MOREL'S, CANAVAN'S *or* MONIZ'S *work.* Including also the cases of slight and early Hfi, the high frequency which we noted is obtainable.

Frequency in Men

The great preponderance of Hfi in the female sex has long been remarked. The statements on the relative frequency in men and women vary in a high degree. SHATTOCK (1913) saw 10 cases in women and 1 in a man among 11 skulls with Hfi. DRESSLER (1927) found 90 per cent. in women and 10 per cent. in men among 71 cases of Hfi. GREIG'S figures (1928) are nearly the same ; among 32 cases there were 28 women and 4 men (about 87·5 and 12·5 per cent. respectively). MOREL (1930) had 15 women and 2 men. MOORE (1935) found 72 cases of Hfi at radiological examinations of 5,955 skulls, among them 70 women and 2 men (97·2 and 2·8 per cent respectively). Among museum material he found that 23 per cent. of the women but only 1·9 per cent. of the men showed Hfi. At autopsies of 1,000 women and men of the same age we found that the frequency of Hfi in women and men is about 100 to 1, these figures according rather well with those of MOORE.

These few cases of Hfi in men are worth special consideration. Even here it may be advisable to separate the cases diagnosed at autopsy from those diagnosed radiologically.

BEADLES' paper (1898) on thickenings of the skull in men does not permit any definite conclusions. The first positive male case of Hfi

seems to have been described by NAITO (1924). It was the case of a man, 50 years of age, who died in a lunatic asylum. He had a very heavy, compact and thick (8 mm.) roof of the skull and, as it seems, pronounced and typical Hfi. Even radiologically Hfi as well as the whole calvaria were dense. Statements on the nutritional state, testes, etc., are missing.

DRESSLER'S large material (1927) contains, besides 64 cases in women, 7 cases in men, which are here summarized and arranged in order of age .—

Case 1 Man aged 47, scanty Hfi, ulcerative endocarditis Case 2. Man aged 52, chronic tuberculosis of the lungs, degree of Hfi not mentioned. Case 3 Man aged 55, ulcerative endocarditis, scanty Hfi. Case 4. Man aged 55, degree of Hfi not mentioned, cancer of the pancreas. Case 5. Man aged 58, degree of Hfi not mentioned, apoplexy. Case 6. Man aged 65, apoplexy, degree of Hfi not mentioned. Case 7. Man aged 70, scanty Hfi, insufficiency of the heart. Statements on the condition of nutrition, testes, etc , are missing in all the cases.

Among the 32 cases of GREIG, 4 men are found with Hfi :—

Case 10 Male aged 60, carcinoma of the œsophagus On each side of the sagittal sulcus a few very shallow, smooth, osteophytic nodules associated with several small excavations of the inner table Case 17. Strong man of temperate habits died, aged 66, of "spastic paralysis." A slight, nodular, osteophytic growth on each side at the level of the frontal tuberosities associated with some pitting in the neighbourhood Case 25. Man aged 66, of average mental capacity , dense, chondrodystrophic skull Atypical, somewhat doubtful case with a thin veneer of bone on the superior face of the small sphenoidal wings and slight nodular osteophytes on the pars frontalis. Case 1 Well-developed man aged 77, carcinoma of the rectum *Osteophytic growth thickens the pars frontalis on either side* The growth is flattened, smooth, hummocky and dense The osteophytes have retained the compact character of the inner table, of which they appear to be an hypertrophy. There are no statements on testes, etc , in any of the 4 cases.

STEWART'S (1928) 2 cases .—

Case 5 Man aged 46, with epilepsy and infantilism, very thick skull with Hfi and increase of the diploe. Weight of the brain 1,460 g Case 6. Man aged 60, melancholic, very stout Skull extraordinarily dense and thick, Hfi Weight of the brain 1,485 g Statements on testes are missing in both cases

Among MOREL'S (1930) 17 cases, 2 were men —

Case 14 Forty-two years old, insane, rather fat on admission to hospital, very emaciated at autopsy, grave pulmonary tuberculosis, typical, rather strong Hfi Weight of the brain 1,200 g Testes completely fibrous (according to MOREL, syphilitic orchitis) Case 13 Man aged 62, with repeated apoplexies, now insane, no glycosuria *Autopsy* Atrophy of the brain, numerous apoplectic foci, severe cerebral and general arteriosclerosis, roof of the skull rather heavy, moderately thick and sclerotic with Hfi.

In the same year REDAELLI describes a typical case of very high degree :—

Man aged 81, moderate structure of the body, with senile marasmus and pneumonia. Marked atrophy of the brain, especially of the frontal lobes, roof of the skull heavy, typical Hfi of very high degree (good illustration). Testes not mentioned.

Among the 660 skulls from the museum which were examined by MOORE, some men with Hfi were found.

A radiologically diagnosed, very interesting case of Hfi in a man, described by SCHIFF and TRELLES, 1931, is referred to above (see p. 15). It might be discussed if the causal connection, stated by both authors, is in fact the real one. Among the 4 cases of FRACASSI and MARELLI (1936) there is a male, 40 years of age, with headache, feeling of thirst, attacks of dizziness and strong Hfi. Neither in both the cases just referred to, nor in the many cases of MOORE and RICHTER, are statements concerning the testes to be found Thus LUCHERINI's Case 7 (1939) is of special interest : a man aged 67 with eunuchoidism and congenital ectopy and hypoplasia of the testicles ; radiologically Hfi, no alteration of the sella. In the large clinical material of KNIES and LE FEVER 4 males with Hfi are found : a body aged 13, two 19 and one 22 years old. Statements on the sexual organs are wanting.

Among the cases of JACOBSEN and NIELSEN there is 1 male psychopath, 58 years old, weight 110 kg., diagnosed as *encephalopathia atrophicans diffusa e hypertensione*. HOLTEN diagnosed Hfi in a neurasthenic man with hypotonia Even in these two Danish cases statements on the testes are missing. OLDBERG found not a single case of Hfi in " normal material " of 897 males between 11 and over 70 years of age.

Our own 9 male cases of Hfi are to be found on pages 50 and 85.

Thus among the cases of Hfi in men diagnosed at autopsy, 25 with fairly explicit clinical and anatomical notes are to be found. Unfortunately in the majority of the cases notes about the testes are missing. Among the cases in the literature, the one case stated by MOREL seems to be the only one : here a total fibrosis of the testes existed. *In our own 9 cases atrophy and sclerosis of the testes of more or less high degree were stated in 6 cases.* In one case endocrinal disturbance, as in CS, and atrophy of the penis were present, but unfortunately the testes were not examined microscopically. In another case alterations of the testes are not improbable, only in 2 cases the testes were morphologically unaltered Thus among the few cases of Hfi in men at least 5 cases with more or less marked alterations of the testes were found. Among the radiologically diagnosed cases of Hfi in man, 12 to date, the testes were examined only in the one case of LUCHERINI ; this was a case of eunuchoidism with hypoplasia of the testes.

These 6 cases of Hfi in men, which are connected with alterations in the testes of marked degree, are of the greatest importance for the theory of MS.

Age

In discussing the age distribution in Hfi it seems advisable to separate the autopsy cases from the purely clinical ones.

In the older preradiological literature only a very few statements on Hfi in women under 40 years are found ; on the contrary it is often stated that the condition occurs in the elderly or very old. The only exceptions which we were able to find in the literature may be mentioned here :—

BEADLES : Woman aged 40, with acromegaly and obesity. *Autopsy :* small, thick exostoses at the inner surface of the frontal bone, large tumour of the pituitary

SHATTOCK : Demented, epileptic woman aged 37, with obesity.

GREIG : Woman aged 35, died of eclampsia after birth of twins. *It may be judged that this is not a case of Hfi but of puerperal osteophyte.*

RITTER : Woman aged 37, weight 175 kg., ovaria gyrata Hypothalamic region microscopically unaltered.

The large material of DRESSLER (1927), including 71 post-mortem cases, contains no less than 16 cases with " hyperostosis of the frontal bone " in the age group 20 to 40 years Looking more closely on these cases, however, it becomes evident that at least 50 per cent. of them were afflicted with commencing or slight " hyperostosis." They died after such conditions as abortion, ruptured tubal pregnancy or ichorous endometritis *Very probably these were not cases of real Hfi but of marked pregnancy osteophyte* DRESSLER himself, however, does not mention this possibility To what extent the always scanty or commencing " hyperostosis " in his other cases of young women was connected with an existing or just completed pregnancy is not discernible from his tables.

A summary of all cases of the literature, with the exception of the author's cases of Hfi described at autopsy, gives the following age distribution :—

Age	11-20	21-30	31-40	41-50	51-60	61-70	71-80	81-90	91-100	Total
Cases	3 (2)	5 (3)	12 (6)	6	29	37	32	13	2	139 (130)

(The enclosed figures are obtained if DRESSLER'S and GREIG'S 9 cases of pregnancy are subtracted)

The table shows quite clearly how rarely Hfi has been described at autopsies on subjects below 50 years of age. If the pregnancy cases of

DRESSLER and GREIG are subtracted, the difference between the ages before and after the climacteric becomes very distinct. It is very possible that the figures of the second and third decades would decline even more if statements on pregnancy were available. The two youngest cases were 20 years old ; before this age no cases of internal hyperostosis have been described at autopsy up to the present.

The author's own material, unfortunately including only 50 autopsies of women in the age period of 25 to 40 years, contains in this period 3 cases of positive Hfi, which were neither pregnant at autopsy nor had been pregnant recently, these cases being recorded on page 41 ; a fourth case with Hfi *and* puerperal osteophyte in a woman aged 30 is described on page 40. Definite cases of internal hyperostosis occurring before the climacteric, and without relation to pregnancy, are thus decidedly rare. Obviously in most of the cases it is a matter of endocrine disturbances ; the literature published until now and the author's own experience up to the present are much too small to permit definite conclusions on the appearance of genuine Hfi in these early decades.

Generally speaking, the cases of Hfi diagnosed only radiologically show a distribution with regard to age which differs considerably from those in autopsy cases. Cases of clinically diagnosed Hfi from the second and third decades are by no means rare here. In the large casuistic of MOORE the cases are distributed throughout the different decades as follows :—

Decade	2	3	4	5	6	7	8	Total
Cases .	2	11	15	16	20	5	3	72

A similar distribution is found in CANAVAN, 1937 .—

Decade	1	2	3	4	5	6	7	8	9	10	
Percentage frequency of Hfi	2·4	4 0	7 3	4·1	4 5	7 4	7 9	1·0	0 9	2 9	
Cases . .	1	3	13	17	26	45	52	48	17	5	Total 227

MORTIMER found a radiological Hfi in a girl aged 18.
ELDRIDGE and HOLM publish a similar table :—

Age .	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80-89	*Total*
Cases	.	6	8	10	9	9	4	4	50

Thus no less than 28 per cent. of the cases are derived from the third and fourth decades.

Conditions similar to these, generally speaking, are to be found in ROSSIER and SECRETAN (1940) :—

Decade .	2	3	4	5	6	7	8	Total
Cases .	2	1	12	9	3	4	...	31

Thus among the 31 cases no less than 24 belonged to ages below 50 years, only 7 women being older.

KIAER (1941) describes 2 cases in women aged 28 and 29, one of them having clinical symptoms for ten years. The paper of KNIES and LE FEVER gives the following age distribution of the cases (5 male cases are included) :—

Decade .	2	3	4	5	6	7	8	Total
Cases	5	5	5	5	3	4	.	27

Thus no less than 20 of the 27 cases belong to the time period from the second to the fifth decades The youngest women were only 13, 16 and 19 years old.

ANDERSEN (1942) describes a radiologically diagnosed Hfi in a woman aged 25. KIRK (1942) saw a case in a woman 25 years old with symptoms since school age. NIEDNER (1943) briefly mentions 2 cases in young women, one of which was a girl aged 16. The age distribution of the cases of GROLLMAN and ROUSSEAU (1944) was as follows :—

Age	20 to 29	30 to 39	40 to 49	50 to 59	60 to 69	Total
Cases .	5	10	16	5	4	40

The youngest was a girl aged 21

Thus on the whole there are no less than 14 radiologically diagnosed cases of Hfi from the second decade in the literature, and about 40 cases between 20 and 30 years of age The age distribution in the autopsy cases, judged by the literature and our own findings, is thus quite different from the radiologically diagnosed cases. It is difficult to see *how this poor agreement is to be explained.* It is not

very probable that the X-ray examination reveals cases of Hfi where the autopsy proves negative.

An exception is formed by OLDBERG's "normal material," showing the following age distribution of radiologically diagnosed Hfi :—

Decade . .	1	2	3	4	5	6	7	8 to 10	Total
Number of the cases	59	69	101	76	78	64	49	50	546
Positive . .	.	.	..	..	3	2	3	11	19
Per cent . .	..	.	..	..	3 8	2 9	6·1	22 0	. . .

Hyperostoses of other types, possibly of endocrine origin, certainly are no rarities, but they must not be mistaken for the genuine Hfi. Our own new material contains, in spite of being rather scanty as regards the first decades, a series of such cases among which some may be quoted shortly: Case 1. Woman aged 22, died of diabetes; peculiar, very small osteophytes, even basal Case 2. Woman aged 24, died of tuberculous meningitis; strong Hfp Case 3. Woman aged 26, died of congenital heart disease; small, heavy, generally thickened skull with white inner surface. Case 4. Woman aged 31 with hyperglycæmia, died of bronchial asthma Case 5. Woman aged 33, died of tuberculous meningitis, thick, heavy skull (400 g.). Case 6. Woman aged 38 with chronic encephalitis; heavy, thick skull (460 g).

Hfi and MS in Relation to Pregnancy

That Hfi would eventually prove to have some relation to the puerperal hyperostosis of the skull, the so-called pregnancy osteophyte, seems already to have been in the mind of ROKITANSKY (1842) and VIRCHOW (1865) and later of RIBBERT (1902) The first to formulate this view seems to have been HARBITZ, who in a discussion (1927) emphasizes that 2 of his 3 cases with Hfi were nulliparæ. DRESSLER in at least 8 cases of young females has described skull changes as Hfi which actually were obvious cases of puerperal osteophytes (p. 102) GREIG (1928), to whom we owe good descriptions and illustrations of the puerperal osteophyte, expresses himself very clearly. Among the 28 women whose skulls showed Hfi, 11 were nulliparæ and 4 uniparæ or multiparæ, while in 13 cases statements about pregnancy are lacking. "There is no evidence that intracranial osteophytes are originated by childbearing and none that normal pregnancy or the normal puerperium stimulates their development." Even NIEUWENHUIJSE (1933) emphasizes that Hfi seems to have no relation to pregnancy. MOORE found among his extensive material that about 50 per cent. of the women with Hfi had been pregnant at least once.

In two studies since 1936 we have emphasized the striking parallelism between the "pregnancy-syndrome" of the young woman and the MS of elderly women after the climacteric. In the former the morphological resemblance between the pregnancy osteophyte and the Hfi deserves notice, although in a considerable number of women with *Hfi, one-quarter to one-third* were *definitely* nulliparæ. Hfi of high degree can occur in nulliparæ, while on the other hand it may be absent completely in women who have had many pregnancies (HENSCHEN, 1937) Even MOREL in 1937 compares Hfi and related disturbances with pregnancy. The alteration in pregnancy is "passager" (transient), in Hfi it is "progressif." MONIZ (1938), obviously misunderstanding the opinion of the present author, declines to entertain any connection between pregnancy and Hfi: "The puerperal osteophytes are ossifications of the dura mater, which have nothing to do with the frontal hyperostoses."

Our material until 1937 decidedly favoured the belief that Hfi *developed independently of pregnancies. Both the age-period relationship* and the occurrence of Hfi in ascertained nulliparæ seemed to exclude any direct correlation between the two conditions Even the histological changes are generally quite different, as is seen from page 21. After this time a few cases were added, which seem to show that Hfi and even the complete MS may exceptionally develop in direct relation to a pregnancy. One of these cases was described by LESZLER *(1940)*: Case 1. Woman aged 31 After childbirth she put on 11 kg. in a very short time and suffered frequently from headache. The bones of the skull radiologically were seen to be thickened, and on the inner surface of the frontal bone a tubercular, irregular hyperostosis was seen Serum Ca and pH normal Another case, which was observed by us, is reported more completely on page 40 · Woman aged 45, III-para, last child seven months before death. Large and stout, strong masculine type of hair-growth on the face, typical Hfi

These two cases go to show that Hfi with adiposity or a complete MS may originate directly from pregnancy, thus recalling the fact that an acromegaly or an acromegaloid condition may follow directly on pregnancy.

In one case in a pregnant woman aged 30 the author saw changes which were interpreted as a slight puerperal osteophyte on the inner surface of a skull with commencing Hfi (p. 63).

C. THE COMPLETE AND INCOMPLETE TRIAD

MORGAGNI'S classical case of *complete MS*, by no means representing a rare constitutional anomaly, in our own experience, has relatively few parallels in the literature, not more than 26 cases with complete

triad being found. (STEWART, 4 cases; MOREL, Case 2; LEVISON, Case 2; SOMOGYI and BAK, Case 1; RADEMAKER, Cases 2 and 3; VAN STEENBERGEN, Cases 3, 4 and 5; ROSSIER and SECRETAN, Cases 6 and 33; KIAER, Case 2; KNIES and LE FEVER, Cases 2 and 4; MCGAVACK and REINSTEIN, 1 case; IVERSEN, 1 case; MELLGREN, Cases 7 and 8; CAMPOS, Cases 2, 3, 7 and 10). In the majority of these the Hfi was diagnosed radiologically, only in STEWART'S, MOREL'S and MELLGREN'S (7 cases) was it confirmed by autopsy.

This survey of the literature gives a rather false impression of the real frequency of the complete triad, as becomes evident in our own examinations. The frequency is much higher; *among our own 266 cases of Hfi no less than 126 (47·4 per cent.) showed a complete syndrome* when slight degrees of Hfi, abnormal hair-growth and obesity are included. Cases with particularly marked features of the complete triad occur relatively seldom even in our own material, as becomes evident more especially from the summary on page 66 The very highest degree of complete MS was observed only three times by us among 700 autopsies (p. 67).

Hfi without Virilism and Obesity

It is not easy to decide how often the principal feature, an isolated Hfi, appears without simultaneous male hair-growth and obesity. There is not much to be obtained from the earlier literature. In papers appearing in recent years such cases are remarkably frequent, but these, being nearly always radiologically diagnosed cases with slight or beginning Hfi in younger individuals (not uncommonly men), must be judged with caution, in our opinion Such cases of Hfi without hirsutism and obesity are mentioned in the material of ROSSIER and SECRETAN and that of KNIES and LE FEVER, moreover, there are cases by VAN STEENBERGEN, LESZLER, JAKOBSEN and NIELSEN, MOLLER, HOLTEN and CAMPOS (Case 9). NIEDNER emphasizes especially that isolated Hfi may occur without hirsutism and obesity. His cases of two young girls were "slender, neat and too young for a Morgagni."

Our own experience tends decidedly to the belief that an isolated Hfi is not so very uncommon. No less than 35 of the 266 positive cases (12 per cent) belonged to this category.

Virilism

The term virilism is here in the first instance to be understood to mean male hair-growth on the face, corresponding to the "virilisme pilaire" of French authors. Coarse male features, big feet and hands, male voice, etc., are especially noted.

About the frequency and the kind of correlation between two such dissimilar anomalies as Hfi and male hair-growth very little has been known up to the present time. In the literature, opinions differ greatly, which is partly due to the fact that virilism, especially hair-growth on the face in women after the climacteric, is obviously very differently assessed. Particularly difficult is it to assess the frequency of slight degrees of pathological hair-growth.

The importance of differences of race and constitutional type have been already emphasized, together with the fact that artificial depilation may lead to false conclusions. Moreover, to this comes the fact that much of the material consists of museum specimens with frequently no note of the age and disease of the patient. Therefore it is not to be expected that a review of the literature in regard to hair-growth will give as valuable results as an investigation of the occurrence of Hfi or obesity.

In the whole literature we were unable to find more than 53 cases of Hfi with particular statements of the hair-growth on the face. Among these cases 37 (nearly 70 per cent.) were more or less hirsute, while in 16 cases the hair-growth on the face was described as normally female.

Putting aside Morgagni's somewhat vague expression, "virili aspectu," Stewart seems to have been the first to describe the combination of Hfi and male hair-growth on the face, though he does not seem to have drawn any conclusions from this.

Morel is at least more interested in the hirsutism, though he does not discuss it in great detail. Anomalies of hair-growth, such as baldness or coarse hairs on the upper lip and on the chin, are not rare in old women. He does not seem to regard the subject as important and does not mention it. Moore simply considers the male hair-growth on the face as a component of his symptom complex.

Among the cases with Hfi and hirsutism the following may be referred to: Levison Case 2, woman aged 57. Rademaker: Case 1, woman aged 53, Case 2, woman aged 40; Case 3, woman aged 50. Van Steenbergen's Cases 2 to 5, women between 38 and 71 years of age. Rossier and Secretan. Cases 6, 18 and 23, age of the patients between 38 and 44 years. Kiaer 3 younger women, aged 23 to 29. Knies and Le Fever · Cases 2 and 4, aged 45 and 41 Stewart (1941), Andersen, Kirk, Melloren (2 cases of women aged 60 and 75). Moller. woman aged 51. Among the 12 cases of Campos, 4 showed a hirsutism of more or less high degree. In Grollman and Rousseau's series hirsutism was observed in 12 out of 42 cases.

In some cases, whether or not hirsutism was present, the patients had features which were male or coarse, while in a few cases the patient had a rough voice.

Somogyi and Bak's Case 1, woman aged 38, likewise showed acromegaloidism, as also Van Steenbergen's Case 3, a woman aged

71, and CAMPOS' Case 7, a woman aged 30. In all 3 cases a complete triad of Morgagni was present.

OLDBERG, finding no relationship between Hfi and hypertrichosis, deems the term MS "inadequate," but, on the other hand, concedes that hypertrichosis in several cases "sign-posted" the diagnosis of Hfi.

Our own investigation on hirsutism in Hfi, as mentioned above, includes even light degrees of increased hair-growth, and showed hirsutism in 184 out of 266 cases, or 69·2 per cent, which accords surprisingly well with the percentage relation stated. In some of our own cases we saw particularly strong eyebrows

Another anomaly of hair-growth, also rather frequently observed, especially in very old women, is the *falling out of the axillary hairs and the falling out or thinning or straightening of the pubic hairs.* Meanwhile, our material not being large and uniform enough to allow positive conclusions, we refer only to the summary on page 70 We have the impression that this anomaly appears rather independently from the Hfi.

We did not see the marked changes in the hair-growth of the head, which is noted by MOREL.

In this connection it is of interest to record that one of our cases of Hfi in men showed distinct anomalies of hair-growth—a kind of *feminisme pilaire.*

Adrenal changes in hirsutism are discussed below.

In certain cases hypogenitalism was observed, which was more pronounced than usual LUCHERINI's Case 7 was eunuchoid, likewise the case of MOLLER. SOMOGYI and BAK published a case concerning a woman aged 38. She was 170 cm in height, weight 116·5 kg., otherwise of pronounced acromegaloid type. Her menstruation began at 9 years of age, later on "she ceased to be a woman, became a sexless monster" KIAER describes a case with Hfi and infantilism

Obesity

A survey of the literature shows soon how often Hfi is associated with some degree of obesity In MORGAGNI's classical case the woman is characterized as "valde obesa." Similar cases are mentioned by BEADLES, SHATTOCK, BONNAMOUR and JAMIN Among the 28 women of GRIEG's large series 3 were very stout (Cases 8, 16 and 22) and 1 was thin, while in the remaining 24 cases no information is available. Meanwhile STEWART was the first to direct attention to the frequent coincidence of Hfi and obesity and to draw positive conclusions from it.

A very exact description of the obesity, together with a discussion of its causation, is given by MOREL, who rightly describes obesity as a remarkably frequent although not constant symptom Like MORGAGNI, MOREL emphasizes that the obesity not infrequently occurs

About the frequency and the kind of correlation between two such dissimilar anomalies as Hfi and male hair-growth very little has been known up to the present time. In the literature, opinions differ greatly, which is partly due to the fact that virilism, especially hair-growth on the face in women after the climacteric, is obviously very differently assessed. Particularly difficult is it to assess the frequency of slight degrees of pathological hair-growth.

The importance of differences of race and constitutional type have been already emphasized, together with the fact that artificial depilation may lead to false conclusions. Moreover, to this comes the fact that much of the material consists of museum specimens with frequently no note of the age and disease of the patient. Therefore it is not to be expected that a review of the literature in regard to hair-growth will give as valuable results as an investigation of the occurrence of Hfi or obesity.

In the whole literature we were unable to find more than 53 cases of Hfi with particular statements of the hair-growth on the face. Among these cases 37 (nearly 70 per cent.) were more or less hirsute, while in 16 cases the hair-growth on the face was described as normally female.

Putting aside MORGAGNI'S somewhat vague expression, "virili aspectu," STEWART seems to have been the first to describe the combination of Hfi and male hair-growth on the face, though he does not seem to have drawn any conclusions from this.

MOREL is at least more interested in the hirsutism, though he does not discuss it in great detail. Anomalies of hair-growth, such as baldness or coarse hairs on the upper lip and on the chin, are not rare in old women He does not seem to regard the subject as important and does not mention it MOORE simply considers the male hair-growth on the face as a component of his symptom complex

Among the cases with Hfi and hirsutism the following may be referred to . LEVISON . Case 2, woman aged 57. RADEMAKER . Case 1, woman aged 53 , Case 2, woman aged 40 , Case 3, woman aged 50 VAN STEENBERGEN'S Cases 2 to 5, women between 38 and 71 years of age. ROSSIER and SECRETAN Cases 6, 18 and 23, age of the patients between 38 and 44 years. KIAER 3 younger women, aged 23 to 29. KNIES and LE FEVER · Cases 2 and 4, aged 45 and 41. STEWART (1941), ANDERSEN, KIRK, MELLGREN (2 cases of women aged 60 and 75). MOLLER . woman aged 51. Among the 12 cases of CAMPOS, 4 showed a hirsutism of more or less high degree. In GROLLMAN and ROUSSEAU'S series hirsutism was observed in 12 out of 42 cases.

In some cases, whether or not hirsutism was present, the patients had features which were male or coarse, while in a few cases the patient had a rough voice.

SOMOGYI and BAK'S Case 1, woman aged 38, likewise showed acromegaloidism, as also VAN STEENBERGEN'S Case 3, a woman aged

71, and CAMPOS' Case 7, a woman aged 30. In all 3 cases a complete triad of Morgagni was present.

OLDBERG, finding no relationship between Hfi and hypertrichosis, deems the term MS "inadequate," but, on the other hand, concedes that hypertrichosis in several cases "sign-posted" the diagnosis of Hfi.

Our own investigation on hirsutism in Hfi, as mentioned above, includes even light degrees of increased hair-growth, and showed hirsutism in 184 out of 266 cases, or 69·2 per cent, which accords surprisingly well with the percentage relation stated. In some of our own cases we saw particularly strong eyebrows.

Another anomaly of hair-growth, also rather frequently observed, especially in very old women, is the *falling out of the axillary hairs and the falling out or thinning or straightening of the pubic hairs.* Meanwhile, our material not being large and uniform enough to allow positive conclusions, we refer only to the summary on page 70. We have the impression that this anomaly appears rather independently from the Hfi

We did not see the marked changes in the hair-growth of the head, which is noted by MOREL.

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in later life in women, who were previously thin or at any rate not fat. In MOREL's series, on the other hand, there are cases without obesity, together with individuals emaciated owing to intercurrent diseases (among 17 cases, 8 were fat, 5 normal and 4 emaciated).

MOORE *occupies himself in his last two studies with obesity in cases* of hyperostoses of the skull, without special reference to the frontal area. The disturbance of fat metabolism which he found in 44 per cent. should therefore be less constant than that of calcium metabolism. In CARR's collection of 17 cases of thickening of the skull, obesity was present in 11 cases.

Descriptions of more or less marked obesity are very frequent. FATTOWICH's 3 cases were exceedingly stout, 120 to 130 kg.

Among the 33 cases of ROSSIER and SECRETAN, 22 had a normal weight, the other 11 were more or less stout, while many without obesity were younger persons. Among KNIES and LE FEVER's 28 cases, 10 were more or less stout. The non-obese cases include younger individuals who form the bulk of this series. CAMPOS' 12 cases showed, *with two exceptions, a more or less pronounced adiposity. In* GROLLMAN and ROUSSEAU's material, obesity was present in 23 of the 42 cases According to TRELLES and MENDEZ the adiposity should disappear in the last stage of the disease. PENDE described both "hypogenital" and "viriloid" adiposity and extraordinary thinness and "disturbances, which recalled neuropituitary cachexia." Even NIEDNER speaks of thinness of pituitary type. OLDBERG's investigation indicates a positive correlation between Hfi and adiposity. This was of general type in the majority of the cases, but 3 to 4 cases showed rhizomelic type.

Even in our own female series Hfi very often is connected with obesity. Among the 266 Hfi-positive cases of Group V., 176 were at the same time more or less stout, corresponding to 66·2 per cent, or one-third of the Hfi cases. Statistically a positive correlation was present In the few cases of pronounced thinness (see table on p. 73) the cause was quite apparent.

Among the 9 *male cases of Hfi*, 3 were very or exceedingly stout, 1 was in good condition, 2 were, in spite of emaciation (cancer), somewhat stout, the remaining 3 were emaciated (cancer and cholecystitis). In some cases the obesity was of explicitly female type.

Summing up, it may be said *that Hfi appears so often in conjunction with virilism and obesity that one is entitled to consider the triad of Morgagni as a biological syndrome, MS.* The table on page 111 gives a clear survey of the conditions found by us in 266 autopsies.

It is rather a formality if the isolated Hfi without hirsutism and obesity is called an incomplete or defective MS · biologically Hfi belongs to the sphere of MS; systematically the Hfi constitutes the main symptom of the MS.

TABLE 25

MS in 266 Post-mortem Cases	Number of Cases	Per Cent
A. Complete triad . .	126	47 4
B. Incomplete triad . .	140	52 6
1. Hfi and hirsutism . .	58	21·8
2. Hfi and obesity . .	50	18 8
3. Hfi solely . . .	32	12 0

D. CLINICAL SYMPTOMATOLOGY

General Statements

MORGAGNI's classical case was a very stout woman, 75 years old, who during her last years had, all in all, been healthy and had never complained either of headaches or of any other discomforts from her head. Death occurred rather unexpectedly while she was at her domestic work. The autopsy showed severe arteriosclerosis and rupture of the heart.

In contrast to this first case, devoid of symptoms, stand the majority of the cases subsequently published, which seem to present a more or less rich and variegated clinical symptomatology. In some of these cases a post-mortem report is available, but the majority are exclusively clinical, so that nothing is known about actual lesions of the brain and other organs

Less frequently cases of MS or Hfi, without connected clinical symptomatology, are to be met in the literature The theme of this chapter will be to examine critically the supposed clinical symptomatology of MS.

When clinical interest in Hfi began, in the last decades of the last century, it was predominantly English and French *psychiatrists and neurologists who tried to find a causal connection between the existing mental or nervous disease and the peculiar alteration of the calvaria.* With others, FOLLIN and DUPLAY (1874), CLOUSTON (1874), and BEADLES (1898) are among these authors

Thirty years later (1928) the important work of STEWART was published which, from the clinical aspect, continues the line of earlier publications. In the work of MOREL (1930) the supposed clinical symptomatology of Hfi achieves more distinct outline In MOREL's opinion, to which many of the later authors subscribed, Hfi and adiposity are connected with a whole series of clinical symptoms,

which are now often summed up in the term, "Stewart-Morel syndrome." Using MOREL's own words, Hfi is "a symptom of disturbed calcium metabolism. It is accompanied by more or less constant symptoms: adiposity of the proximal parts of the extremities and of the intestines, generally developing late in the disease . . . disturbances of sleeping, insomnia, nocturnal agitation; sometimes *polyphagia, polydipsia and urinary disturbances. It is able to provoke* secondary symptoms (headaches, tardy epilepsy). It seems to be part of an ensemble of infundibulo-tuberic symptoms, which in some cases are anatomically verifiable."

After MOREL's monograph followed some clinical papers by VAN BOGAERT (1930), by SCHIFF and TRELLES, and by ALMQUIST (both 1932) and STERTZ (1934). In the following two years the important works of MOORE were published.

While MOREL is chiefly interested in Hfi, MOORE's researches include all forms of cranial hyperostosis: "The symptom complexes of the several types (of hyperostosis) are closely allied, and in the future they may be proved to be identical. . . . The fact that the hyperostoses coexist in the same persons and that the skulls are generally thickened in cases of all types sustains the view that though morphologically distinct, all types have the same fundamental etiology, this is indicated also by the related clinical phenomena." These clinical symptoms correspond very much with those described by MOREL: calcium metabolism disturbance, obesity, disturbance of equilibrium and gait, muscular weakness, easy fatigue, dimness of vision, occipital diplopia, headache, epileptiform seizures, neuralgia, nervousness, tendency to worry and depression, impairment of memory, weakness of the seventh nerve, difficulty of speech, mental slowness, dementia.

CARR (1936) found nearly the same phenomena. obesity in 64·7 per cent, menstrual disturbances in 76·4 per cent., weakness in 58·8 per cent, visual disturbances in 41·1 per cent, headache in 82·3 per cent., convulsive seizures in 35·3 per cent, mental changes in 58·8 per cent, difficulties of memory in 88·2 per cent., dizziness in 64·7 per cent

A similar, more or less complete or distinct symptomatology is to be found in the exclusively clinical cases of FRACASSI and MARELLI (1934), *JAMES (1936), SOMOGYI and BAK (1937) MOREL (1937)* emphasizes that it is not by mere chance that Hfi is found chiefly in asylums for the insane and in neuropsychiatric clinics, where it seems to be more frequent than anywhere else. DELMAS-MARSALET (1938) and LEHOCSKY and ORBAN (1938) endorse this opinion. "We must consider the term 'syndrome' correct and justifiable from a clinical viewpoint."

MONIZ (1938) defends energetically the Stewart-Morel syndrome. in his opinion there exists, in fact, a certain symptomatology which

establishes "a characteristic and special syndrome" or "a real autonomic disease." Infundibular symptoms such as polydipsia and polyphagia, disturbances of sleep, further mental disturbances, arteriosclerotic dementia, melancholia with dementia and epileptic dementia are almost constant in this disease. There are also very few cases without appreciable mental disturbances, but more or less accentuated mental disturbances are not lacking in the evolution of Hfi. It is an example of a rare disease which predominantly is to be found in asylums for the insane.

The survey of the literature also discloses numerous authors of a later date who more or less unreservedly set up a distinct clinical syndrome connected with Hfi. BARTELHEIMER was specially interested in the eventual coincidence of Hfi with disturbances of the carbohydrate metabolism, and he tries to prove that Hfi often may be closely connected with a pituitary diabetes.

Of special interest is the work of ROSSIER and SECRETAN, which includes a clinical-radiological series of 39 cases of hyperostosis, including 32 cases of Hfi, all without autopsy. In their opinion cranial hyperostosis—not only Hfi—is a well characterized syndrome, which can be suspected clinically and whose diagnosis may be confirmed radiologically. The symptomatology, the abnormal glucose tolerance curve, the specific dynamic effect of the proteins, the adiposity, the amenorrhea, the disturbances of sleep and the hypercholesterolæmia speak for an infundibulo-pituitary disturbance, which even has its beginning in adolescence

In the ample, also exclusively clinical-radiological, series of KNIES and LE FEVER (1941), which includes 28 cases of which younger male and female patients form a great part, the symptomatology is essentially the same as above

Even the 12 cases of CAMPOS (1943) and the 42 cases of metabolic craniopathy examined by GROLLMAN and ROUSSEAU (1944) are exclusively clinical-radiological. The symptomatology is on the whole the same as *in the cases of* MOREL, MOORE, ROSSIER and SECRETAN, and KNIES and LE FEVER

Finally, OLDBERG (1945) has examined the supposed clinical symptomatology of Hfi "The Hf and t[illegible]
thickening of the c[illegible]
dizziness, and pr[illegible]
syndrome' seems thus to be justified. . . . The occurrence of dizziness and headaches does not correspond to an increase in blood pressure" OLDBERG was above all interested in the disturbances of the carbohydrate metabolism in cases of Hfi This will be discussed more closely later on

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In somewhat sharp contrast to these authors others now maintain *that Hfi may occur without special symptoms. Hfi is not connected with a special symptomatology and is not sufficiently defined or confirmed to warrant the setting up of a special Stewart-Morel syndrome.* A large number of cases with post-mortem examination which can show distinct organic alterations will be of special importance.

The first representative of this opinion after MORGAGNI seems to be GREIG (1928) "*Intracranial osteophytes are harmless* and symptomless and have no relation whatever to either syphilis or insanity." In the same year HELLMER expressed a similar opinion. Clinical symptoms were in no case directly attributable to Hfi.

According to REDAELLI (1931) Hfi may occur in connection with different complexes of disease, especially in mental diseases. This association with various other diseases is, however, accidental. According to him Hfi is a non-specific process, sometimes a simple symptom of old age. Its occurrence in connection with a number of disturbances of endocrine or infundibulo-tuberal origin does not justify the creation of a special syndrome in the sense of MOREL. NIEUWENHUIJSE (1931) defends the same opinion : there exists no distinct connection between the clinical phenomena and Hfi. Even HARBITZ (1935) expresses himself in the same direction · the Hfi is "undoubtedly of little significance from a purely clinical standpoint."

In a series of publications (1935-45) the present author subsequently contended for the opinion that Hfi represents "a symptomless, rather frequent alteration in elderly women, standing in no direct relation to the different symptoms enumerated by MOREL", therefore it is "neither necessary nor justified to set up such a syndrome. The 'Stewart-Morel syndrome' is to be regarded as a construction which is founded on an incomplete knowledge of the occurrence, origin and importance of Hfi" (1935).

SCHNEIDER (1936) is sceptical in his opinion of the Morel syndrome : "In the former conception of the symptomatology of Hfi the radiological changes of the bone are wrongly placed in the foreground*, the symptomatology is rather dominated by degenerative senile alterations of the brain and probably even of the pituitary body"

According to DONINI (1937) the mental disturbances are said to be neither constant nor characteristic, although the headaches are said to be directly related to the disease. SOMOGYI and BAK (1937) accentuate the fact that the Stewart-Morel syndrome is not accompanied by a specific neuropsychiatric complex of symptoms. The psychical troubles should not be considered as a direct consequence of the cranial alteration.

CANAVAN (1938), examining a series of autopsies on 3,250 insane persons, described Hfi in 230 cases. It is very clearly evident from

his table that Hfi by no means corresponds to a certain form of psychosis :—

Senile dementia	41
Dementia præcox	54
Epilepsy	14
Feeble-mindedness	23
Maniac-depressive	18
Arteriosclerotic psychosis	27
Alcoholism	11
Other psychoses	26
Dementia paralytica	16
Total	230

He adds that patients with Hfi are rarely recorded as complaining of subjective symptoms such as fullness, headache, or a feeling of heaviness or pressure in the head. He was unable to record any correlation between clinical observations and any constantly associated pathological change

VAN STEENBERGEN (1938) conforms more to the opinion of GREIG : "The syndrome of Morgagni may develop without any complaints, but by its very nature is often accompanied by the incommodities of old age"

In a case of MS with various symptoms examined by REIDER (1938), the left frontal lobe showed findings characteristic of Alzheimer's disease. The wall of the III-ventricle, mentioned by MOREL to be the site of characteristic lesions, in this case showed no unusual changes.

FUMAROLA (1939) emphasizes that "the series of cases consistently devoid of symptoms in spite of existing considerable endocraniosis is too large." According to him, Hfi is sometimes found in persons with persistent headache, but also, on the other hand, "often in patients who never have suffered from headache."

KORPASSY (1939) had 5 autopsy cases of MS In none of these did any of the phenomena described by the neurologists exist.

LUCHERINI (1939) is of the opinion that Hfi mostly manifests itself without endocrinal disturbances and with clinical signs of minor importance, which in all probability are connected with the age of the patients, with the cerebral arteriosclerosis and with the concomitant arterial hypertension.

ELDRIDGE and HOLM (1940) found at radiological examination of a large psychiatrical series of 200 women 50 positive cases of Hfi. Hfi was, as the table shows, not connected with a special form of psychosis. "It therefore appears obvious that the occurrence of hyperostosis frontalis interna does not have any close or significant relationship to any one particular mental disease" Obesity was present in only

8 of the 50 cases, visual disturbances were completely absent, headaches occurred in 3 cases, other neurological symptoms, except epilepsy and paralysis, were lacking. It was therefore impossible for the authors to concur in the opinion that a definite syndrome, sometimes referred to as "the triad of Morel," was present in these cases of Hfi, at least so far as the female population of a mental hospital is concerned.

Dementia præcox, hebephrenic	11
,, ,, *catatonic*	4
,, ,, paranoid	5
Psychosis with cerebral arteriosclerosis	11
Senile psychosis	4
Involutional psychosis	2
Manic-depressive psychosis	5
Paranoid state	2
Psychosis with somatic disease	1
Paralysie générale	2
Epilepsy	1
Mental deficiency	1
Undiagnosed psychosis	1
Total	50

Hemphill and Stengel (1940) say: "From the psychiatric and neurological point of view the disease is still insufficiently defined. . . . The existing literature contains no symptom that could be described *as pathognomonic,*" but "*it appears justifiable to conclude that in* advanced cases some form of mental disorder is a part of the syndrome"

Jensch (1941) considers the varying clinical aspect to be "surprising and inviting scepticism . " He continues · "Here, as *often in rare and etiologically indistinct cases, much must be subtracted* which can be freely explained in terms of the age of the patient or because of the occasional coincidence" The only certain fact, however, seems to be the frequent observations of psychic disturbances , while, *as to the causal connection (with Hfi), it is necessary to give full weight* to such considerations as præmorbid personality, heredity, as well as the mental disease of the climacteric and later stages of life "

Roth (1941) expresses himself very distinctly . " It was felt that the *neuropsychiatric signs and symptoms were not attributable to the* effect of the hyperostoses on the underlying brain tissue but were the result of other factors, such as cerebral arteriosclerosis, hypertension, etc."

Andrews (1942) emphasizes that the surveys of radiological and museum material have shown that Hfi may be present without any symptoms, the patients dying from some unrelated disease. It seems clear from published observations that Hfi is often present for a long *time before any further symptoms develop.*

Especially important are two post-mortem cases of "Stewart-Morel's syndrome," examined by MELLGREN (1942) and referred to in the survey of the literature. In neither of these cases could it be determined that the cerebral disturbances might have been provoked directly by pressure from the frontal enostoses. Nor was it possible to prove any other connection between the mental symptoms, the condition of the brain and the endocrine habitus. MELLGREN concludes "that *the 'Stewart-Morel syndrome' has no uniform genesis*" (italics by M.).

To this series belong also SCHMIDT'S, PEDERSEN'S and WISSENBERG'S cases (pp. 34 to 35).

Finally, stress may be laid upon the present author's series of 76 cases of Hfi of high degree, or complete MS, which at autopsy often showed an anatomical basis for the clinical symptoms. We refer to pages 42 to 48

Is Hfi connected with a Special Symptomatology?

If patients affected with Hfi do show clinical symptoms, the following possibilities may in our opinion be discussed :—

1. Hfi causes a compression of the brain, that is, increases the intracranial pressure and thus provokes symptoms
2. Hfi is in itself clinically more or less symptomless but constitutes a part of an endocrine syndrome with characteristic symptoms ; as a radiologically determinable indicator of this disturbance, it is of clinical and diagnostical significance.
3. The clinical symptoms often occurring in cases of Hfi are mainly symptoms of old age, senile diseases, arteriosclerosis, hypertension, obesity and diseases of the brain of different kinds

In the literature of the subject representatives of all these opinions are to be found

1 *Hfi itself gives symptoms of compression*

NAITO (1924), to whom we are indebted for a fundamental, anatomical and radiological examination of Hfi, emphasizes its tumour-like character According to him, clinical symptoms of an increase of the intracranial pressure do exist, producing especially headaches or sometimes epileptic seizures

In his monograph (1930) MOREL lists a series of symptoms which he considers to be secondary to Hfi, among them the following : headaches, the character of which he describes more closely , late convulsive crises, sometimes extremely violent, limited to the face, the arms or to one part of the body, which he describes as epilepsy , finally, perversion of the sense of smell and acoustic hallucinations Hfi can have an effect on the dura, on the mass of the brain proper and on the intracranial pressure. These cerebral symptoms are not very constant nor must Hfi always produce remarkable symptoms In later work

from the year 1937 MOREL expresses himself more reservedly: Hfi does not give its own special symptoms, those observed seeming to have their origin in the cerebral affection itself. "Perhaps one must make an exception for the headaches which at the beginning and during the development of Hfi are extremely frequent. These headaches are frontal and less violent than in a leptomeningitis. They are likened to a sense of heaviness in the head." That MOREL connects the headaches causally with Hfi is to be seen by the fact that he recommends a surgical intervention with removal of the excrescences in grave cases.

According to STERTZ (1934) the effect of Hfi on the brain would be easier to understand if one accepts a "directed pressure on the brain in the sense of G. HERMANN." Hfi should be able to develop pressure in the direction of the base of the brain.

According to JAMES (1936), who also supposes a compression of the brain to occur, "operation is indicated when the hyperostosis gives rise to signs or symptoms of increased intracranial tension or focal effects."

Even MOORE (1936) thinks that Hfi by its volume may provoke symptoms, and he recommends surgical treatment in suitable cases.

In one case of RADEMAKER (1938) such an operation was performed with apparent success

SOMOGYI and BAK "saw a case of Hfi in which headaches were added as a secondary symptom." To them it seemed probable that Hfi had been the cause of conversion neurosis with aggravation and fixation of certain symptoms.

According to MONIZ arteriography shows the independency of Hfi to the atrophy of the brain; although part of the symptomatology can be explained by a marked compression of the brain by Hfi.

HEMPHILL and STENGEL think that "in certain cases mental symptoms may be secondary to the mechanical effect of bony changes on the brain." PENDE (1940) defends the same opinion. KIAER (1941) meanwhile conceives Hfi to be a change belonging to the disturbances of metabolism. Even MOLLER (1942) thinks that Hfi may produce serious consequences by compression, though relatively seldom.

We have ourselves consistently given expression to the opinion that Hfi is hardly capable of provoking special symptoms *Having regard to the great capacity of the brain mass for plastic adaptation to slowly growing, expansive, non-inflammatory processes, it is hardly to be expected that Hfi, even if a considerable flattening of the frontal poles exists, would be able to provoke cerebral phenomena.* Rightly, SCHNEIDER compares Hfi with the osteoma, which "hardly ever, even in cases of actual extension into the interior of the skull, provokes phenomena of compression of the brain."

2. *Hfi is of clinical importance, not in a symptomatological sense but because it is an indicator of endocrine disturbances.*

As has already been said, MOREL recognises certain symptoms to be secondary to Hfi. According to him the symptomatology is supposed to be due mainly to changes in the infundibulo-pituitary region, which in his opinion explains not only Hfi and adiposity, but also the polydipsia, polyphagia, polyuria, disturbances of the sleep rhythm and visual disturbances of many patients. SCHIFF and TRELLES, among others, seem to share this opinion, and MOORE presents a similar point of view, though he also postulates a compression effect due to the Hfi.

RICHTER (1939) decidedly declines to suppose any mechanical compression and seeks the cause of the phenomena in the disturbance of the endocrine regulation. ROSSIER and SECRETAN, ANDERSEN, JACOBSEN and NIELSEN, and GROLLMAN and ROUSSEAU seem to defend this opinion

To this group of authors even OLDBERG belongs. "The occurrence of local frontal hyperostosis and to a certain degree even a diffuse thickening of the calvaria in women as well as in men, affords an opportunity for delimiting a special form of diabetes possibly of pituitary type."

3. The third possibility, indicated above, that *the clinical symptomatology in cases of Hfi is provoked chiefly by diseases of old age, obesity, hypertension and organic alterations of the brain,* has already been discussed explicitly on pages 114 to 117, so it need not be taken up again at this point

Subjective Symptoms

Headaches differing in kind, intensity and localization are among the most frequent phenomena in patients with Hfi In CARR's series no less than 83·2 per cent. were affected by headaches RICHTER found constantly frontal headaches while, on the other hand, only 3 of ELDRIDGE and HOLM's 50 patients had this symptom. Very often no other symptom beyond these persistent pains, chiefly in the forehead, lead to an X-ray examination and the discovery of Hfi It seems very remarkable that symptoms of discomfort, often progressive, not uncommonly had already begun in adolescence, in some cases probably years or even decades before the occurrence of Hfi. In a 30-year-old woman, examined by MONIZ, the headaches began at puberty. In a 50-year-old patient, examined by BARTELHEIMER, severe pains had already begun at the age of 20. In ROSSIER and SECRETAN's material the headaches play a very important rôle , in no less than 7 cases the symptom had existed since childhood, surely long before the formation of Hfi. In 3 of the cases a sinusitis was present, in 2 cases the pains seem to have originated after encephalitis, while in a further case there was a glioma of the occipital lobe. In GROLLMAN and ROUSSEAU's series, headache was encountered in only 19 out of 42 patients.

In not a few cases the headaches dated from an accident or after an operation, for instance, KNIES and LE FEVER, Case 20, woman, 30 years old, and REIDER, Case 2, woman aged 40, fourteen years previously suffered a very severe head trauma in an accident, followed by unconsciousness of several weeks' duration, headaches, change in personality.

According to OLDBERG, " Hfi and, to a certain extent, the general thickening of the calvaria can be co-ordinated with dizziness and probably with headaches."

Not uncommonly a marked hypertension existed simultaneously, for example, KNIES and LE FEVER, Case 1, 66-year-old woman with vertigo, frontal headache, ataxia, loss of memory, suggesting cerebral vascular accident ; IVERSEN, 40-year-old woman, with very severe headaches and hypertension ; JACOBSEN and NIELSEN, 42-year-old woman, etc.

Some authors lay stress upon the importance of the hypertension in the symptomatology ; this is especially the case with LUCHERINI. Even we ourselves described in many cases the combination of Hfi with headaches and hypertension. OLDBERG's opinion is, on the contrary, that the occurrence of dizziness and headaches does not correspond to an increase in blood pressure.

In two of RADEMAKER's cases, one a woman of 32 and the other 40 years of age, the headaches were associated with vomiting; in a third case they came in the form of attacks. In these cases, as in some others in which women before the climacteric were affected, one is apt to think of megrim In SOMOGYI and BAK's Case 1 the patient had had attacks of megrim since her thirteenth year.

Thus headaches occur very frequently in Hfi but are not of uniform type. MOREL notes that he was not able to identify their character more closely. In his monograph (1930) he has emphasized that they are extremely frequent in the course of Hfi, especially at the beginning. They are likened to a sensation of heaviness in the head

Headaches of this vague type, however, occur in so many quite different circumstances that it is hardly possible to attribute to them any great diagnostic importance, and therefore we are inclined to agree with LUCHERINI, who in most cases of Hfi saw headaches and dizziness, which he attributed as being due in all probability to the age of the patients, with the cerebral arteriosclerosis and with the concomitant arterial hypertension

Of the same nature is the *dizziness*, which is so frequently recorded in the medical reports. CARR found dizziness in 64·7 per cent. of his cases of hyperostoses of all types According to BELLONI this symptom shares with Hfi a foremost position in MS

In the majority of the cases with both these subjective symptoms, being exclusively clinical cases without autopsy, it is necessary to be all the more cautious in judging their clinical-diagnostic importance because, in our experience, organic alterations of the brain in these old

patients are extremely frequent. In MELLGREN'S Case 8, in which dizziness was also an associated symptom, the post-mortem examination revealed a serious chronic-degenerative affection of the cerebellum.

Neurological and Psychiatric Symptoms

In cases with Hfi nervous and mental disturbances of every sort play an important rôle. *Impaired memory* seems to be nearly as frequent as headaches CARR'S figure is as high as 83·2 per cent. in his cases of cranial hyperostoses of all types. MOORE, likewise, emphasizes it. Other examples are DONINI'S Case 1 and KNIES and LE FEVER'S Cases 1, 4 and 12.

Muscular weakness is often noted (in CARR'S summary 58·8 per cent. of the cases) as also *asthenia* and *neurasthenia* , for instance, cases of MOREL, MOORE, PENDE and many others such as cases of DONINI (stout woman, 55 years old), SOMOGYI and BAK (somewhat stout woman aged 52, twenty-two years ago psychiatric trauma, weak, weeps, hypochondriacal, impulsive thoughts), LEHOCZKY and ORBAN (neurasthenia), RADEMAKER'S third case, LUCHERINI (79-year-old woman with hypertension 230/110), CALABRESE (33-year-old man, weight 138 kg.), KIAER, JACOBSEN and NIELSEN (Cases 2 and 9), and HOLTEN (man, 33 years old, with hypotension, perspiration and palpitation of the heart). MOREL mentions visual disturbances ; MOORE, dimness of vision and occipital diplopia ; CARR found visual disturbances in no less than 41 per cent ; CASATI and RADEMAKER also mention it. Among other neurological symptoms occurring in cases of Hfi may briefly be mentioned here tremor, intention tremor, ataxia, dysarthria, paresthesias, neuralgias of different kinds, deafness, hallucinations.

A great number of authors have recorded convulsive or epileptiform seizures (MOREL and MOORE, among others). CARR found seizures in no less than 35 per cent. of the cases, ROSSIER and SECRETAN observed epilepsy in 3 cases (12, 18 and 33). In DONINI'S third case, a 60-year-old woman, myoclonus-epilepsy was present in addition to depression, dysarthria and mental defect of high degree, the section showed atrophy of the cerebral hemispheres

Sleep disturbance is one of the commonest symptoms, mostly in the form of sleeplessness, sometimes nightly restlessness or, again, somnolency, inverted sleep rhythm or nocturnal agitation DONINI observed somnolency in a 53-year-old schizothymic patient, and CALABRESE in a 33-year-old man with hypogenitalism and obesity. JACOBSEN and NIELSEN observed nocturnal agitation in a 64-year-old patient. Among other authors referring to sleeplessness are LEHOCZKY and ORBAN, ROGER, TROELL, ROSSIER and SECRETAN (in 11 of their cases, another 4 showing alternating sleep), KNIES and LE FEVER and IVERSEN (40-year-old woman with a hypertension of 220 and diabetes),

and JACOBSEN and NIELSEN (Case 3, 58-year-old woman with obesity and, besides other symptoms, sciatica.)

In many cases there are reports of depression, mutism, deep melancholy, anxiety, thoughts of or attempts at suicide. Symptoms of this kind are not uncommonly combined with other serious neurological or mental alterations. CARR speaks of mental changes in 58·8 per cent. of his cases. It would be too great a digression to recount further detailed references.

Recognized mental diseases play an important rôle in the supposed symptomatology of Hfi, as witness the tables of CANAVAN (1938) and ELDRIDGE and HOLM (1940). According to PERKINS and BIGLAN the psychosis often passes into dementia; according to TRELLES and MENDEZ it often ends in gross confusion; according to MONIZ, who emphasizes the nearly constant mental disturbance, chiefly of the nature of arteriosclerotic dementia or melancholy with dementia or epileptic dementia, the syndrome carries the gravest possible prognosis. *Thus the psychical condition which is said to be connected with Hfi and MS seems to be extraordinarily varied.*

In the opposite camp there are often authors who deny that Hfi is in any way responsible for the neuropsychiatric symptoms which may be present or who emphasize the scarcity of psychiatric symptoms. Among them especially GREIG affirms that Hfi has nothing to do with mental insanity, FATTOVICH and LUCHERINI are of like opinion In KORPASSY'S 5 cases neurological symptoms were lacking. Since 1935 we ourselves have repeatedly supported a similar opinion, which is suitably illustrated by the table of our results on pages 42 to 48.

Somatic Symptoms

Blood Pressure, Weight of the Heart—For good reasons one may suppose that already in MORGAGNI'S classical case a symptom which is not seldom connected with MS could have been stated—the hypertension The 75-year-old stout patient died of rupture of the heart with hemopericardium From the post-mortem report we know that she suffered from severe arteriosclerosis, and although it is hardly more than a supposition we may suppose that she suffered from hypertension, eventually [illegible]

The earlier literature [illegible] could elucidate this question, b [illegible] blood pressure can be collected from the last ten years In the great majority of these Hfi has been diagnosed radiologically without autopsy con- [illegible] From Diagram 13, showing [illegible] blood pressure and age, it [illegible] f them may be classed as hypertensives. The numerical preponderance of the cases with hyper-

tension becomes evident, especially after 50 years of age. Those patients who could be called more or less stout are distributed in a rather similar way. Among the 32 cases with notes on the state of nutrition 22 belonged to the hypertensives, 10 were individuals without increased blood pressure.

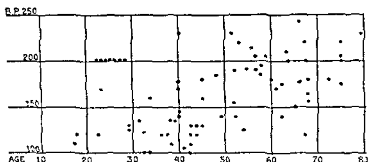


DIAGRAM 13

Distribution of cases with Hfi in literature with regard to blood pressure and age

These conditions correspond well with our own experiences. As is evident in Diagram 12, page 80, hypertension and hypertrophy of the heart are frequently occurring changes in Hfi.

Disorders of the Carbohydrate Metabolism—Observations on diabetes, glycosuria and hyperglycæmia in Hfi are not uncommonly found in the literature after 1930. In a 34-year-old woman with Hfi, obesity and anomalies of hair-growth, MOREL found a temporary polyuria and glycosuria. CASATI mentions a blood sugar of 190 mg per cent. in a 50-year-old stout woman with Hfi. EISEN (1936) stated actually diabetes in a 54-year-old woman with Hfi, obesity and hypertension. In 2 cases of LUCHERINI a disturbance of the carbohydrate metabolism was present: Case 1, a woman aged 66, with very pronounced Hfi, hypertension and diabetes, and Case 6, a woman aged 75, with Hfi, hypertension and glycosuria PENDE emphasizes that the occurrence of diabetes mellitus and insipidus is of special interest in Hfi In a moderately stout woman with Hfi, KNIES and LE FEVER found, amongst other symptoms, polydipsia, polyuria and occasional glycosuria. In a case, described by IVERSEN, a 40-year-old stout woman with Hfi, virilism and hypertension (220) had actual diabetes. NIEDNER found diabetes in a patient who was radiologically diagnosed as Hfi but showed no other endocrinological signs. Other cases of diabetes mellitus in Hfi are described by FRACASSI and MARELLI, TAGER, SHELTON and WATZEN, BERT and GADLEWSKI, cited by CAMPOS, who himself observed 2 cases—1 and 2—of Hfi with temporary glycosuria without hyperglycæmia.

Besides these case reports interesting studies by CARR (1936),

and JACOBSEN and NIELSEN (Case 3, 58-year-old woman with obesity and, besides other symptoms, sciatica)

In many cases there are reports of depression, mutism, deep melancholy, *anxiety, thoughts of or attempts at suicide.* Symptoms of this kind are not uncommonly combined with other serious neurological or mental alterations. CARR speaks of mental changes in 58·8 per cent. of his cases. It would be too great a digression to recount further detailed references.

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The earlier literature on Hfi contains hardly anything which could elucidate this question, but about 90 cases of Hfi with notes on blood pressure can be collected from the last ten years. In the great majority of these Hfi has been diagnosed radiologically without autopsy confirmation, which is only available in 3 cases From Diagram 13, showing the distribution of these cases according to blood pressure and age, it can easily be seen that more than half of them may be classed as hypertensives. The numerical preponderance of the cases with hyper-

and Hfi-negative women. In both categories the frequency should be somewhat lower than in men. In the clinical examination of a woman, 55 years of age, with MS and hypertension and with a fasting value of the blood sugar of 110 mg. per cent, the curve progressed normally with a maximum of 181 mg. per cent. and a hypoglycæmic phase of 89 mg. per cent after three and three-quarter hours.

At this point the not infrequent references to polydipsia and polyuria may be noted. MOREL sometimes found a transitory polydipsia and polyuria, and other references are those of FRACASSI and MARELLI, DONINI, MONIZ, and ROSSIER and SECRETAN.

As to the possible correlation between the male hair-growth on the face and the disturbance of the carbohydrate metabolism in MS, no investigations are available in the literature. The summary of our own results appears on page 82

Blood Cholesterol—Estimations of the blood cholesterol in MS have been scanty and somewhat contradictory. ROSSIER and SECRETAN examined 8 cases of Hfi and found the following values which—with two exceptions (Cases 20 and 33)—may be called high or pathologically increased.

No.	Age	Blood Pressure	Cholesterol	Cholesterol Esters
				per cent
11	78	170	234	
15	43	130	421	75
16	31	135	282	73
17	56	245	266	
20	38	110	155	67
23	38	135	421	73
30	44	220	302	64
33	43	110	141	64

In 4 cases which he examined, CAMPOS, on the other hand, found values which lie within the normal range

No.	Age	Blood Pressure	Cholesterol
2	80	150	140
3	48	170 to 200	170
10	42	190	180
12	67	220	180

GROLLMAN and ROUSSEAU estimated the blood cholesterol in 18 cases and found variations between 180 and 220 mg. per cent

The great difference between ROSSIER and SECRETAN's values,

BARTELHEIMER (1939), ROSSIER and SECRETAN (1940), ANDREWS (1942) and OLDBERG (1945) on the disturbance of the carbohydrate metabolism are available. CARR found that there was an increase in sugar tolerance. BARTELHEIMER, in a series of papers, came to the conclusion that diabetes in MS is to be understood as being of central, probably pituitary, origin and that "the occurrence of Morgagni's triad with insulin-resistant diabetes seems to be of fundamental importance." According to BARTELHEIMER one is entitled "to suppose a close connection between Hfi and pituitary diabetes."

ROSSIER and SECRETAN examined blood-sugar curves after ingestion of glucose in 21 cases of Hfi and 3 cases of other forms of cranial hyperostosis. In 10 cases they found a somewhat flat curve of otherwise normal configuration. The reactive hypoglycæmia was mostly only slight The condition resembled somewhat that found by LICHTWITZ in endogenetic adiposity and diseases of the diencephalon (flat hyperglycæmical curve; excessive hypoglycæmia of long duration). According to ROSSIER and SECRETAN these changes in the glucose tolerance curves as well as other disturbances in Hfi indicate an infundibulo-pituitary alteration.

In a case of Hfi in a somewhat stout 45-year-old woman with "narcoleptic attacks" and heavy frontal headaches, ANDREWS found, during the attacks, a blood sugar of 130 mg per cent.; in tolerance curves the following values were found Fasting, 150 mg. per cent.; after one hour, 210 mg. per cent , after two and a half hours, 190 mg. per cent.

CAMPOS observed only 2 cases of temporary glycosuria among his 12 cases of Hfi and, in view of the great frequency of diabetes, considers its appearance in conjunction with Hfi as a mere coincidence

GROLLMAN and ROUSSEAU found hyperglycæmia in only 5 instances (2 of them with mild glycosuria and in 3 cases relative insulin resistance). In 12 other patients the dextrose tolerance did not differ from that observed in other obese individuals.

OLDBERG is of the opinion that Hfi and, to a certain degree, Hcd affords an opportunity for delimiting a form of diabetes with the following characteristics: (a) A benign course, not uncommonly with spontaneous remission, (b) little tendency to acidosis and thus a negligible risk of coma, (c) requiring insulin exclusively in a few cases who have been ill for several years, (d) a decrease in sensibility to insulin. In these cases OLDBERG discusses "the possibility of an extra-insular diabetes, especially of pituitary origin."

A summary of our own experiences, unfortunately restricted to the occurrence of major disturbances such as diabetes, glycosuria and hyperglycæmia, is to be found on page 80. To judge by this summary, one would not expect to find much difference in regard to major disturbances of the carbohydrate metabolism between Hfi-positive

and Hfi-negative women. In both categories the frequency should be somewhat lower than in men. In the clinical examination of a woman, 55 years of age, with MS and hypertension and with a fasting value of the blood sugar of 110 mg per cent., the curve progressed normally with a maximum of 181 mg. per cent. and a hypoglycæmic phase of 89 mg. per cent. after three and three-quarter hours.

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GROLLMAN and ROUSSEAU estimated the blood cholesterol in 18 cases and found variations between 180 and 220 mg per cent.

The great difference between ROSSIER and SECRETAN'S values,

which are often very high, and the moderate or, at least, not high ones of CAMPOS is remarkable, but may perhaps only be due to the use of *different methods. Only 2 of our cases have a known cholesterol level:* Group VI, Case 3, 55-year-old-woman, blood pressure 230, blood cholesterol 216 mg. per cent.; Case 4, 60-year-old woman, blood pressure 185, blood cholesterol 277 mg. per cent.

The nature of this hypercholesterolæmia, so often recorded and so reminiscent of Cushing's syndrome, has not invited much comment up to the present time. ROSSIER and SECRETAN designate it as a sign of an infundibulo-pituitary disturbance, but we should like to recall the fact that a hypercholesterolæmia may occur in various circumstances, *as in diabetes, gravidity, arteriosclerosis and hypertension.* Three of ROSSIER and SECRETAN's cases (11, 17 and 30) and our own 2 cases were women with marked hypertension

Blood Calcium—GREIG was the first to discuss the blood calcium in Hfi. He bases the discussion on the morphological similarity of Hfi to the puerperal osteophyte, of which he says: "We need not demand a hypercalcæmia in puerperal osteophytes; further research may show that there is" In his opinion Hfi develops in a similar way: "Senility is said to lead to a decalcification of the skeleton; and with rapid decalcification or diminished excretion of calcium a hypercalcæmia may perhaps result, which in turn may be an important factor in the formation of Hfi Intracranial osteophytes are concomitant with advancing years and always associated with absorption of calcium from the bones locally and/or generally. . . Intracranial osteophytes are the outcome of disuse-absorption from the bony skeleton of calcium and phosphorus salts in excess of the existing excretory powers." GREIG does not seem to have examined the skeleton for osteoporosis or calcium content, and statements on blood calcium in Hfi are also lacking in his study.

MOREL also regards Hfi as being a symptom of disturbed calcium metabolism, without giving evidence of his opinion. According to MOORE, "it is . . a reasonable supposition that it is a disorder of calcium metabolism in which that mineral is present in excess in the organism"

Determinations of the blood calcium have been done by different authors and may be arranged in tabular form (p. 127)

Taking the normal concentration of the blood calcium as 9 to 11 mg. per cent, most cases in the table show normal (18 cases) or somewhat low (14 cases) values, whilst increased values are found in only 3 cases.

Blood Phosphorus—In LESZLER's first case the value was normal. ROSSIER and SECRETAN found generally low or very low values in 11 of their cases of Hfi · in 4 of the cases the value was below 3 mg per cent. (2·3 to 2·5), in the remaining 7 cases it was between 3·1 and

3·7 mg. per cent. In 1 case of CAMPOS the value was 3·2 per cent. All the values may be considered normal. GROLLMAN and ROUSSEAU found normal values in 26 cases.

TABLE 26

Author	Case	Age	Blood Ca	Note
CARR	.	..	Normal	.
EISEN	..	45	"Low"	..
LUCHERINI	1	66	10 5	.
	3	47	11 8	.
	4	57	11 2	..
	5	43	9 2	..
	6	75	10 0	..
	7	67	12 2	Male
	10	79	9 6	..
	11	67	10 7	.
FATTOWICH	3	46	Normal	.
RADEMAKER	1	53	11 0	.
	4	41	11 2	
LESZLER . . .	1	31	Normal	.
ROSSIER and SECRETAN .	3	24	9 8	..
	11	41	0 1	..
	12	17	19 2	..
	15	43	9 5	
	16	31	9 5	
	17	56	9 8	
	19	36	10 7	.
	20	38	9 6	
	24	50	9 8	.
	26	43	9 1	
	27	59	11 4	.
	29	62	9 2	Male
	30	44	10 0	
	33	43	10 1	
	34	18	9 6	.
	37	36	10 2	
	39	40	9 7	.
HEMPHILL and STENGEL .			Increased	
ROTH . . .		.	Increased	
CAMPOS	12	67	10 0	
GROLLMAN and ROUSSEAU	26 cases		Normal	
HENSCHEN	4	60	9 8 to 10 1	

Blood Phosphatase—The first estimations of blood phosphatase in Hfi are to be found in the papers of ROGERS. He found no change from normal. In CAMPOS' Case 7 the value was 6·5, which must be considered as being somewhat low (normal, 10 to 20 U.K)

Basal Metabolism—Some authors have measured the metabolism in MS or Hfi. CARR found that there was a low basal metabolic rate. SOMOGYI and BAK found in their first case a value of +1 per cent. BARTELHEIMER gives normal values. ROSSIER and SECRETAN nearly always found values which were within the normal limits, in only

3 cases (16, 17 and 26) was the basal metabolism distinctly increased. KIAER found 103 to 117 per cent. in a 29-year-old woman and in a 23-year-old one 122 to 153 per cent. CAMPOS notes in Case 1 – 19 per cent., in Case 2 + 10 per cent., in Case 9 – 5 per cent. and in Case 12 – 3 per cent. In 2 cases at our disposal (in Group VI) the basal metabolic rate was estimated. In Case 2 – 15 per cent. was recorded and in Case 4 + 7 per cent. GROLLMAN and ROUSSEAU also investigated basal metabolism and in most cases found variations within + 10 or – 10 per cent. of the normal. The variation in these values hardly allows any conclusion to be drawn.

In 16 of their cases, among them 14 with Hfi, ROSSIER and SECRETAN examined the specific-dynamic effect of proteins and found in 10 cases normal values, in 4 cases a relatively mild and in 2 cases a rather intense reaction.

The 17-ketosteroid content of the urine, which seems to be of considerable significance in the diagnosis of CS and disorders of the adrenal cortex, was examined in 10 of GROLLMAN and ROUSSEAU'S patients. The excretion was 3 to 7 mg., entirely within the normal limits.

Prognosis

Some authors venture to express an opinion on the prognosis of Hfi or MS. MONIZ (1938) says that adiposity disappears as the disease develops, whilst the general disturbances remain and the prognosis of the syndrome is, at least for the present, "tout à fait mauvais." According to KIAER (1941) the prognosis is rather bad. Some cases may remain stationary but others will progress, and the disease may end in enormous adiposity and complete dementia ANDERSEN (1942) regards Hfi as being a serious endocrine disorder in younger women

E. THERAPEUTICS

Before 1935 the treatment of the presenting clinical features in MS and Hfi seems to have been purely symptomatic, but in the last ten years attempts have been made in several countries to influence the supposed symptomatology of these pathological conditions by more fundamental therapeutics. Two methods are available. medical treatment or surgical intervention

MOORE (1936) confesses to therapeutic difficulties : "There is no specific treatment yet in view, but there are, however, certain rational indications upon which treatment can be based These are of two orders : measures to combat the metabolic imbalance, where the existence of such can be established, and measures which are to be considered as local treatment of Hfi."

Some authors recommend a hormonal treatment. ROGER had treated a 52-year-old woman with considerable Hfi, obesity and headaches symptomatologically without success, after which he was successful with gynergen therapeutics. He does not mention which symptoms were alleviated, but the effect of gynergen upon headaches is well known. MONIZ (1938) had no success with endocrine treatment or radiotherapeutics.

ROSSIER and SECRETAN (1940), who acted upon the view that MS is an infundibulo-pituitary disorder, used preglandol (Hoffman-La Roche) in several cases, mainly intramuscularly, in increasing doses until 1 to 2 c c. were given four times weekly, this treatment also causing slight anaphylactical reactions. Two cases were refractive but, on the other hand, 3 cases were favourably influenced, menstruation became regular, the subjective symptoms and sleep disturbances ameliorated. Some other cases which were not so fully described showed that preglandol has a favourable influence on the symptomatology of the Hfi.

Brief mention may here be made that BENNHOLD (1940) has also reported on successful treatment of CS with ovarian hormone and thyroid preparations.

BERBLINGER, who, generally speaking, is sceptical of the supposed symptomatology of MS, writes in 1943 : " In so far as therapeutics are necessary at all in this connection, an attempt could be made to diminish the functions of the anterior lobe of the pituitary by means of sex hormones."

Among other therapeutic measures which have been tried by different authors there may be mentioned CARR (1936), amino-acetic acid by feeding large quantities of gelatin daily; TRELLES and MENDES (1939) recommend a symptomatic treatment of the disturbances of calcium and fat metabolism; PENDE (1940) has tried a very complicated treatment with success—parathyroid hormone by mouth together with calcium-ionophoresis by the transoculo-occipital route (according to BOUGIGNON), which has caused the headaches to disappear; while for viriloid obesity, thyroid hormone and folliculin in high doses are given, and for insufficiency of the pituitary body, hormone of the anterior and posterior lobes

MOORE (1935) had already discussed surgical intervention in the case of signs of increased intracranial pressure as a result of hyperostosis, while in 1936 he recommended surgical treatment in cases of psychical manifestations which might progress to dementia, " it appears that much good might be accomplished by turning down the frontal bone flap."

JAMES (1936) and MOREL (1937) share a like opinion but, on the other hand, MONIZ seems to decry surgical treatment.

RADEMAKER (1938) was probably the first to operate on a case of Hfi : it was the case of a 53-year-old woman with a psychosis

(melancholia, paranoid ideas, mutism, negativism). At trepanation a typical Hfi which had been radiologically diagnosed was revealed. This was chiselled off and the bone flap was replaced. After the operation there was a "considerable amelioration." According to JACOBSEN and NIELSEN (1942) even in Denmark there is to be found a certain experience in the surgical treatment of Hfi. However, further notes on the results obtained are not available.

It is no wonder that the treatment should be so much in the dark, for the etiological factors of MS and Hfi have been so scantily analysed (JENSCH).

F. PATHOGENESIS OF FRONTAL HYPEROSTOSIS

General Statements

Before discussing the different theories of the pathogenesis of Hfi *it is necessary to submit the general normal and pathological changes of the roof of the adult and senile skull to a closer analysis. A comparison of the frontal hyperostosis with other more or less similar formations of new bone on the inner surface of the skull also sheds valuable light on the problem.*

Apart from individual exceptions the youthful brain and skull stop growing between the twentieth and twenty-fifth year of life. Already at this stage the appearance of the calvaria varies, because the shape, thickness and weight of the skull as well as the thickness of the tables and the density of the diploe vary individually At later ages the skull has therefore acquired a highly individual shape, which is in part *genetically conditioned, but for the rest apparently also depends* on mechanical and endocrine influences.

The general senile changes of the calvaria, which, in my opinion, have been all too little considered in the discussion of the pathogenesis of Hfi, were observed as early as 1828 by BROUSSAIS. He wrote: "The brain cannot sink together and concentrate on itself without being followed by the cranium To this is due the separation of the inner table from the outer, as the latter is less disposed to follow the brain when it draws back" A similar argument was also advanced by SOMMERING (1844).

SAUVAGE (1870) went into the matter at greater length. He stressed —quite rightly, as a fundamental point—that the normal and the pathological lie very close to each other in the ageing organism; "... l'état physiologique et le pathologique sont si voisin l'un de l'autre, qu'il est souvent bien difficile de tracer la ligne de séparation entre les deux"

Atrophy of the brain causes a change of shape and an atrophy of the skull: "Owing to the extensive shrinking of the brain .. the

cranium becomes deformed: the resulting condition is senile atrophy." [1] According to SAUVAGE this atrophy is much more pronounced in women than in men: "We have observed that in women the predisposition to atrophy here discussed is at least three times as great as in men." And he writes, with regard to the thickness of the senile skull and its different layers: "In old age the two layers sometimes increase in thickness at the expense of the diploe—the commonest condition—while in other cases the cellulæ of the diploe increase in volume. As regards the thickness of the cranial tables it varies considerably in later ages, so that we may find either hypertrophy or atrophy of the cranial tables." A final passage would seem almost to refer to the thickenings to be found in frontal hyperostosis: "formed by the increase in thickness of the bone by means of new bone formation on the interior surface of the bone."

In 1890 HUMPHRY gives pregnant expression to practically the same views:—

> "It is well known that shrinkage of the brain substance, associated with old age, general wasting or prolonged alcoholism, is commonly attended by an increase of fluid in the meshes of the pia mater or a thickening of the calvarial part of the skull or with both these conditions. . . . The thickening of the skull wall in old people takes place chiefly, if not exclusively, on the interior, and is commonly first and most marked beneath the domes of the frontal bone, on the two sides of the median line, over the part of the

STROEBE (1903) draws especial attention to the "malleability" of the skull even in adults —

> "The change of shape develops through disappearance of bone substance on the one side and new formation of bone on the other . . A decrease of the skull content, owing to total or partial inhibition of the development of the brain or to shrinkage or atrophic processes in the brain, may entail a diminution of the cranial cavity However, if a compensatory hydrops *ex vacuo* develops during the shrinkage of the brain, this diminution of the cranial cavity may fail to appear The reduction of volume, whether it consists in a local, partial or general narrowing, is in the adult skull caused by deposits of bone on the interior of the skull, especially beneath the domes of the frontal and parietal bones, so that a thickening and sclerosis (concentrical accommodative hypertrophy) of the bone, at first not accompanied by any pronounced change of the outer shape of the skull, may develop. . . In many cases the decrease in volume is affected principally by the inner table of the cranial bones, but advances gradually over the air-containing bone cells in the anterior and medial cranial grooves concentrically into the interior of the skull, during this procedure the air cells may increase enormously in size. . . The perpendicular part of the frontal bone over

[1] Translated (like the following quotations) by the present author.

(melancholia, paranoid ideas, mutism, negativism). At trepanation a typical Hfi which had been radiologically diagnosed was revealed This was chiselled off and the bone flap was replaced. After the operation there was a "considerable amelioration." According to JACOBSEN and NIELSEN (1942) even in Denmark there is to be found a certain experience in the surgical treatment of Hfi. However, further notes on the results obtained are not available.

It is no wonder that the treatment should be so much in the dark, for the etiological factors of MS and Hfi have been so scantily analysed (JENSCH).

F. PATHOGENESIS OF FRONTAL HYPEROSTOSIS

General Statements

Before discussing the different theories of the pathogenesis of Hfi *it is necessary to submit the general normal and pathological changes of the roof of the adult and senile skull to a closer analysis. A comparison of the frontal hyperostosis with other more or less similar formations of new bone on the inner surface of the skull also sheds valuable light on the problem.*

Apart from individual exceptions the youthful brain and skull stop growing between the twentieth and twenty-fifth year of life. Already at this stage the appearance of the calvaria varies, because the shape, thickness and weight of the skull as well as the thickness of the tables and the density of the diploe vary individually. At later ages the skull has therefore acquired a highly individual shape, which is in part genetically conditioned, but for the rest apparently also depends on mechanical and endocrine influences.

The general senile changes of the calvaria, which, in my opinion, have been all too little considered in the discussion of the pathogenesis of Hfi, were observed as early as 1828 by BROUSSAIS. He wrote: "The brain cannot sink together and concentrate on itself without being followed by the cranium. To this is due the separation of the inner table from the outer, as the latter is less disposed to follow the brain when it draws back" A similar argument was also advanced by SOMMERING (1844)

SAUVAGE (1870) went into the matter at greater length. He stressed —quite rightly, as a fundamental point—that the normal and the pathological lie very close to each other in the ageing organism. "... l'état physiologique et le pathologique sont si voisin l'un de l'autre, qu'il est souvent bien difficile de tracer la ligne de séparation entre les deux."

Atrophy of the brain causes a change of shape and an atrophy of the skull: "Owing to the extensive shrinking of the brain ... the

of the atrophy of the brain" According to REICHARDT it is neither macroscopically nor microscopically possible "to determine even approximately whether a certain calvaria was equally thick at the beginning, or whether it thickened only because of the pathological processes in the brain."

SCHLESINGER (1914) speaks only in general terms: "The cranial bones pass gradually through considerable changes which engage the sutures, but also the shape and structure of the bones"

Concerning the questions here discussed, THOMA's (1916-17) detailed investigations into the growth of the skull and its disturbances only show that the histomechanical examination of the skull is in many respects still rather deficient as THOMA himself says. He nevertheless considers it "probable that further investigations into the hyperostosis may succeed in devising a method of measuring the pressure relations between the skull wall and the brain." The following observation by THOMA is rather interesting from our point of view, *i.e.*, that the impressions and ridges on the interior of the skull develop because "the pressure exerted on this surface by the convolutions varies in degree." Other "tensions, deriving from the traction of muscles and gravitation," are also of importance in the development and height of the ridges. THOMA's purely mechanistic point of view will be discussed below.

A work of especial importance for the present problem is that published by LOESCHKE and WEINNOLDT (1922). After the first stage of growth, and after a stage of equilibrium in the cerebrocranial system between the ages of 20 and 30, there begins eventually a third stage, characterized by a senile decrease in volume of the brain.

"For a time this is undoubtedly compensated for by an increase in the fluid content of the ventricles, the soft membranes and the subdural space, but the skull, too, shows a very lively reaction, we find a great deal of deposition of parallel lamellæ on the inner table The laying down of bone is, however, limited to certain regions, namely, exclusively, to the parts which form the calvaria, while resorptive processes can be observed both before and afterwards at the base The reason for this localization is as follows As soon as the brain becomes smaller than corresponding to the volume of the skull, it sinks downwards with its whole weight into the cerebrospinal fluid and presses on its basal surfaces, while the space above it is filled up with cerebrospinal fluid, which is, however, exposed to a constant resorption pressure, and it is in this way that a pressure release develops on the interior of the calvaria This seems to be most effective in the regions where the dura is but loosely attached to the skull, here the most pronounced deposition of bone sets in while the areas in which the dura adheres to the sutures, the falx or around the arteries show comparatively little proliferation.

THOMA criticized LOESCHKE and WEINNOLDT's statements in a later work, claiming that it is necessary to differentiate between the

the supraorbital ridges upwards and laterally may also often have a double wall and contain air-filled cavities. In such cases the tabula interna, arched above the cavum cranii, often shows a distinct and deep impression of the adjacent surface of the brain: depressions correspond to the convolutions, while sharp and pointed bone ridges outline the grooves. In this way and by *this concentric accommodative atrophy of the bone*[1] a picture of the interior surface of the bone may develop similar to that found in eccentric atrophy due to brain pressure "

STROEBE apparently gives no special data on the frontal hyperostosis proper, and the long quotation, translated into French in MOREL'S work (who for the rest quotes from DIETZ) seems to refer to other types of bone changes.[2]

BERNSTEIN, too, touching briefly on this displacement of the two *tables towards the brain, speaks of a concentric atrophy of the skull* roof—as ERDHEIM remarks, this does not apply to the senile hyperostotic skull roof, where the bone certainly is displaced towards the interior of the skull, although it does not become atrophic but hypertrophic instead. By simply substituting "skull" for "skull roof" the expression, "concentric atrophy," becomes justified.

In a work on progressive paralysis ALZHEIMER (1904) deals with the transformation of the skull. He found thickening of the skull roof and substitution of the diploe by compact bone tissue in 18 of 31 cases, further in 5 of 7 cases of senile dementia, in 4 of 5 cases of chronic alcoholism (the last-mentioned cases showed signs of being incipient stages of dementia præcox), in 2 of 5 cases of epilepsy and in 5 of 16 cases of cerebral arteriosclerosis. According to these findings a thickening of the skull wall with an accompanying disappearance of the diploe can be observed in many mental diseases with atrophy of the brain

REICHARDT (1906) and his pupils SUESSE and MEYER (1908) and SIPPEL (1909) made further investigations into the skull changes in atrophy of the brain. REICHARDT is very sceptical of the opinions of the earlier authors, quoted above. He replies in the negative to the question whether there occurs a secondary accommodative concentric hyperostosis of the skull bones subsequent to a primary atrophy of the brain in cases of paralysis "When comparing the volume of the skull and the weight of the brain and, on the other hand, the weight and volume of the calvarial bones, it seems quite improbable that the calvarial bones have a tendency to thicken secondarily in consequence

[illegible] STROEBE [illegible]

[illegible] station
[illegible] F. H.]
[illegible] crane
[illegible] "Und
man kann . . . von lokaler, excentrischer, accommodativer Atrophie [illegible] licized by F. H.] des Schadels sprechen." MOREL'S conclusion: "STROEBE . . ." is therefore unjustified.

women than in men, "the condition must be due to a disorder of some structure peculiar to the female which is as yet unknown" (MOORE, 1936)

MORTIMER'S (1937-38) investigations into the rôle played by the hypophysis in changes of the skull shed a new light on the pathogenesis of diffuse osteoporosis, sclerosis and thickening of the skull. *Demineralization* (osteoporosis simplex) was found in the cranial skiagram of animals after treatment with thyroid by mouth or pituitary thyrotropic hormone by injection A similar result was seen after prolonged administration of adrenotropic hormone in young animals, but there is doubt as to the specificity of this effect. *Cranial sclerosis* was best seen in the calvaria, frontonasal angle and tympanic bulla, after prolonged dosage of parathyroid hormone. Sclerosis was also produced by prolonged administration of crude alkaline anterior lobe extracts, above all, in hypophysectomized animals. This was particularly true as the animal became resistant to the ketogenic effect of such hormones; such sclerosis was associated with marked obesity. This last happening is of special interest as affording a possible explanation for the high frequency of the association of cranial sclerosis and adiposity in women.

After examining radiologically 494 "dysplastic" skulls, 63 per cent. of which were female, MORTIMER classified them into four types of "dysplasia," two of which were indicative of hyperfunction of the anterior lobe and two of hypofunction.

	Cases.	Males	Females
Group I— Hyperfunction Acromegaloid dysplasia. (In this group 75 cases of the age of 17 years and under—42 males and 33 females.)	274	57 per cent.	43 per cent.
Group II— Hypofunction, possibly following over-activity. Sclerosis	130	10 „	90 „
Group III— Hyperfunction Dwarfs . .	19	10	9
Group IV— Hypofunction. Sclerosis .	71	5	66
Total	494	..	.

The sclerosis present in the two related Groups II and IV was about ten times as frequent in women as in men, and is, according to

senile involution of the skull and hyperostosis of the cranial bones. THOMA, too, considered the first as the consequence of a decrease in volume of the brain, while hyperostosis of the skull, lying beyond the region of physiological processes, should be derived from the diminution of the critical value of the tension of the material.

In a study of the senile changes in the roof of the skull, ERDHEIM (1935) agrees with LOESCHKE and WEINNOLDT.

"Like the normal thickness, the degree of thickening of the skull roof

shr [illegible] of the calvaria in which the [illegible] nam, although there is a dis[illegible] he inner table more than the outer, which explains why the bone increases in thickness.

This dislocation of the inner table towards the brain is due to a formation of new bone in the dura, with bone lamellæ and cement lines. ERDHEIM reproduces a very good picture. His work is, for the rest, filled with interesting observations, which, however, we lack space to discuss in detail.

Our own investigations into the histology and histogenesis of the senile roof of the skull completely confirm ERDHEIM's results.

It has long been known that thickened skulls, sometimes light and porous, sometimes heavy and sclerotic, may be found not only in old people but also sometimes in younger individuals before the age of 50, and especially in women. Nevertheless a closer analysis of the different morphological shapes and the causative conditions was lacking until about twelve years ago (1935-36). It is therefore to MOORE's credit to have undertaken the first great elucidatory survey of the various diffuse types of hyperostosis. MOORE differentiates three types among the more or less diffuse hyperostoses: nebula frontalis (frontal cloud), Hcd and Hfp. The nebula frontalis appears as a triangular or ovoid area of density and thickness in the squama frontalis. It is a process limited to the diploe, thus leaving the tables unaffected and therefore not always visible from the interior at autopsy. Nor does the [illegible] here to do with general sclerosis [illegible] ie diploe, and often accompanied [illegible] MOORE the Hfp—in our opinion a rather common type—is the least definite and most infrequent. The diffuse hyperostoses, as Hfi, being incomparably more frequent in

was also first suggested by CLOUSTON. It recalls an older theory concerning the development of the pregnancy osteophytes, also mentioned briefly by LOESCHKE and WEINNOLDT. According to this theory, and in spite of nothing being known of any decrease in weight of the mother's brain, the thickening of the inner table, occurring during pregnancy, was considered to be probably the consequence of a decrease in volume of the brain, "which is, however, in any case as regards pregnant women, not the only factor which elicits proliferation of the bone," as hormonal stimuli can be taken into consideration. Even according to NAITO (1924) Hfi is at first "a substitute for the space which has developed through atrophy of the brain"; sometimes, however, the enostosis looked more like tumour formation. DRESSLER (1924) explains the remarkable frequency of hyperostosis in old women by referring to the early and more marked onset of senile atrophy of the brain in women He believed that he had found an important contributory factor in the *sinking back of the brain during prolonged stay in bed*, which might alone, even when there is no distinct atrophy, exert "a sufficient pressure-releasing effect on the superimposed bone." DRESSLER also draws attention to the bone changes during pregnancy, which likewise might play some rôle in the development of hyperostosis. REDAELLI (1931), LASERRE (1934) and GESCHICKTER and COPELAND (1936) adopt CLOUSTON'S, NAITO'S and DRESSLER'S theory, which will henceforth be called the *compensation theory.*

This theory, which had many supporters, was doubted by various investigators—for instance, by GREIG (1928), who considered it "*more than doubtful*," and by STEWART, who very rightly stressed the infrequency of extreme hyperostosis as compared with the frequent occurrence of senile atrophy of the brain. In a later work STEWART also denies that, in Hfi, reduction of the volume of the brain stimulates the deposition of new bone on the inner table of the frontal bone. STERTZ, too, rejects the theory of a secondary hyperostosis subsequent to an atrophy of the brain, in his opinion the Hfi is "primary." According to MONIZ the cause of Hfi is independent of atrophy of the brain, whereas, on the other hand, Hfi may itself exert a considerable pressure on the brain

Our own investigations point in the same direction as those carried out by GREIG and STEWART The tables on page 73, where the case reports from Groups III and V are recorded, seem to indicate fairly definitely that there is no direct correlation between Hfi and atrophy of the brain. In several cases extreme hyperostosis is found together with a normal or even great weight of the brain, but there are also many cases with pronounced atrophy of the brain without any trace of hyperostosis. If atrophy of the brain were in any way connected with hyperostosis, such a correlation might either consist in the atrophy's facilitating the development of hyperostosis, or perhaps more probably in *a common*

MORTIMER, a sign of hypofunction of the pituitary, accompanied by a well-marked disturbance of carbohydrate and fat metabolism. In both groups the sclerosis correlated closely with obesity. MORTIMER also suggests that it is here not infrequently a familial genetically conditioned anomaly, a familial dyspituitarism; he also points out that the cranial dysplasia is of considerable diagnostic value in the clinical recognition of pituitary function in the individual.

Summing up the above discussion we find that there are two factors which especially elicit diffuse changes of the skull—a mechanical one, i.e., atrophy of the brain, and an endocrine, more or less polyglandular, factor. These two principal factors are actually not so opposed as it might seem; the atrophy of the brain is itself clearly to a great extent of endocrine origin. Besides these two principal factors a third one must be mentioned, viz., the genetic factor, which will be discussed below.

The Pathogenesis of the Frontal Hyperostosis

MORGAGNI, whose detailed description was quoted in the introduction, restricts himself to a pertinent, purely formal, genetic observation: "Omnia ex substantia erant magis alba, quam in toto cranio, ut ex nova osseæ substantiæ accessione, & quasi effusione facta esse viderentur." He does not say anything as to the origin of this new formation of bone tissue

ROKITANSKY and VIRCHOW, too, discuss only the morphogenesis of the Hfi, which they consider to be "the result of an increase in bone formation without any known reason."

The various theories regarding the *pathogenesis of frontal hyperostosis* have all been published during the last fifty years. It is not difficult to distinguish between the following *eight principal theories*:—

1. *Hyperostosis is the result of repeated congestion in the insane*—This theory was first advanced by CLOUSTON (1896)—his patients suffered from "alternating insanity" BEADLES (1898) and SHATTOCK (1913) agreed with CLOUSTON's view of the importance of periodical congestion. We will henceforth call this theory *the congestion theory*. It seems to be nearly exclusively based on observations of insane individuals. As Hfi is by no means found exclusively in such autopsy materials, but also in mentally completely normal subjects who never suffered from any congestion, this theory need not be discussed any further.

THOMA, too, believed that "in the circumscribed local hyperostoses . . . it was mainly local disturbances of the circulation and innervation" which came into consideration. This theory, too, has no real foundation in fact.

2. *Hyperostosis is to be considered as a compensatory new formation of bone in senile atrophy of the brain.* Like the preceding theory, this one

here lead to the breaking up of the connection between the dura and the frontal bone.

SCHNEIDER considers this theory "not quite satisfactory, though exceedingly probable," and reminds his readers of THOMA's histo-mechanical investigations into the growth of bones, and particularly the skull. On the other hand, THOMA does not dwell long on the effect of traction but discusses mainly the importance of load and pressure.

MONIZ is a convinced supporter of MOREL's theory regarding the importance of the pull exerted by the dura.

4. KNAGGS and various Italian authors, *e.g.*, BERTOLOTTI, NICOTRA, DONINI, PENDE, FUMAROLA and others, connect Hfi with sinusitis, "endocranitis" and "endocraniosis," as well as with pachymeningitis, osteitis, "osteosis," "neurohypophysitis" and other similar conditions originating in the accessory sinuses of the nose. As real inflammatory changes have apparently never been observed here, and as terms like "endocraniosis" and "osteosis" scarcely correspond to any exact conceptions, we do not find it necessary to discuss these theories.

5. Some authors interpret Hfi as a *syphilitic change.* LERI and COTTENET found, in the Musée Dupuytren, a series of syphilitic skulls with Hfi. BERTELOT and PENDE hold the opinion that the simultaneous occurrence of syphilis and Hfi is not accidental. ARCHANGELI interprets Hfi as a sign of congenital lues, and DEFRANCO considers it very probable that syphilis may bring about this hyperostotic process. In the light of our present knowledge it seems unnecessary to discuss these assumptions further. Even GREIG denied it categorically.

6. Nor does another opinion, suggested by BONNAMOUR and JAMIN as well as by PICARD, viz., that Hfi represents a local *Paget-like change* in the bone, require any further discussion. The histological pictures lend no support whatever to such an assumption.

7. Hyperostosis is, above all, the *expression of a disturbance of the calcium metabolism.* This theory was first suggested by GREIG (1928) and afterwards taken up and modified by MOREL and MOORE. In 1935 MOORE characterizes the frontal hyperostosis "as a disorder of calcium metabolism in which that mineral is present in excess in the organism." Later experiments, aiming at demonstrating some definite metabolic disturbances, did not, however, yield any positive results (MOORE, 1936). ROTH (1941) conceived of a newer, more complicated calcium theory —

"Cross-section of the calvarium gives the impression that there has been a deposition of calcium salts on the endocranial surface of the internal table in the affected regions with subsequent stimulation of the activity of the neighbouring osteoblasts, so that new bone is formed. The passage of large amounts of calcium salts into the cerebrospinal fluid and through the [illegible]

the flow of the cerebrospinal fluid is likely to be slowest, and where there

causative factor eliciting both atrophy of the brain and frontal hyperostosis. The higher frequency of senile atrophy of the brain in women has long been well known and Hfi occurs nearly exclusively in women. It is, nevertheless, rather far-fetched to assume a compensatory new formation of bone in the shape of frontal hyperostosis in cases of atrophy of the brain. As mentioned above, the shrinkage of the brain elicits other changes of the skull.

DRESSLER'S suggestion that the *sinking back of the brain through prolonged stay in bed* was of importance does not seem very well founded Apart from the fact that bedridden people may change their position frequently and lie now on one side, now on the other, and that in many patients the forehead is not at all the highest point of the skull, clinical investigations show that many patients with Hfi have only been confined to bed for a very short time. Even if we assume an extremely rapid development of the bone formation on the inner table—which is not compatible with the histological picture, however—we are certainly not justified in connecting Hfi with the stay in bed. It must also be borne in mind that Hfi attacks women almost exclusively, which makes this last-mentioned theory completely worthless.

3. *Hyperostosis is the response to the formative stimulus caused by the traction of the adherent dura.* This theory was proposed by MOREL in 1930. In his opinion the weight of the brain and of the cerebrospinal fluid was transferred to the dura ; the ridges and impressions on the interior of the frontal bone were arranged exactly according to the play of the forces of traction. To this local factor must be added a further etiological one of the nature of a general endocrine disturbance (see below). This theory will henceforth be called the *traction theory.* It has some points in common with DRESSLER'S theory that the origin of hyperostosis should be sought for in the patient's prolonged stay in bed. In my opinion MOREL and other authors have misinterpreted the reason for the conspicuous adherence of the dura to the inner table. The adherence of the dura to the inner table implies, as stressed by ERDHEIM, primarily the existence of a highly increased *biological* connection between the bone tissue of the frontal bone and its periosteum, the dura. We find such an intimate connection of periosteum and bone tissue wherever new formation of bone is going on. It may be observed at the inner table of the skull when the brain and the skull are growing—in youth—or again when the bony skull once more must adapt itself to the shrinking brain. There is no doubt that the hyperostotic inner table resembles to a certain degree the uneven nodular insertions of tendons and muscles to the bones , this does not justify the assumption of traction exerted by the adherent dura, however. In this connection the two briefly mentioned cases of cerebral tumour (p 64) are very instructive , the erosion of the inner table, caused by the chronically increased intracranial pressure, can

here lead to the breaking up of the connection between the dura and the frontal bone.

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"Cross-section of the calvarium gives the impression that there has been a deposition of calcium salts on the endocranial surface of the internal table in the affected regions with subsequent stimulation of the activity of the [illegible]

the flow of the cerebrospinal fluid is likely to be slowest, and where there

would be increased opportunity for sedimentation to occur. In cases of Morgagni's syndrome accompanied by hypertension and arteriosclerosis it may be assumed that there is increased permeability of the blood-brain barrier, but another cause must be sought for this in those cases in which there are no changes in the circulatory apparatus. In such instances endocrine factors appear to be responsible for the increased permeability. . . . In this connection it is interesting to refer to BENDA's work, showing that an increase of the permeability of the barrier between blood and cerebrospinal fluid sometimes occurs during pregnancy. This is probably of significance in the formation of 'puerperal osteophytes' of the skull during pregnancy, and lends support to the hypothesis here advanced for the formation of the hyperostoses of Morgagni's syndrome. The evidence for the relationship of barrier permeability to menstruation and ovarian function suggests at least a partial explanation for the preponderance of the incidence of Morgagni's syndrome in females."

Against the calcium theories of GREIG and MOORE we might in the first place raise the objection that they do not answer the question why a general disturbance of calcium metabolism should cause new formation of bone so specially localized as, for instance, Hfi.

GREIG's analysis is, in my opinion, not very convincing :—

"The formation of intracranial osteophytes is an innocuous relief to a system supersaturated with calcium, brought about in an area which age renders least important and which has the necessary blood supply for the nourishment of bone-forming cells . . Intracranial osteophytes are the outcome of disuse-absorption from the bony skeleton of calcium and phosphorous salts in excess of the existing excretory powers. . . . Should failure of locomotion be but slowly progressive, the excretory organs sufficiently eliminate the reabsorbed salts of calcium and phosphorus, and intracranial osteophytes are not formed"

MOORE interprets the frontal hyperostosis as "a disorder of calcium metabolism in which that mineral is present in excess in the organism"; this disorder sets in after the cessation of "menstruation, gestation and lactation. In a second paper he is already more reserved : "The ultimate causation of calvarial hyperostosis . . is conjectural. . The 6 cases in whom intensive clinical studies have been made have *not* established that there is a clear-cut metabolic disorder . . . serum calcium and phosphorus have shown no change . . . it appears that the condition must be due to a disorder of some structure peculiar to the female which is as yet unknown." In his third and last work on this question MOORE also is very reticent · "The evidence is that the condition is a metabolic disease in which, as far as is known at present, fat and calcium metabolism only are at fault . . The disorder at present cannot be considered as part of any of the endocrine diseases as such diseases are at present known."

To this should be added that the numerous determinations of the calcium values in the blood published up to now nearly always show normal values (p. 126) Against ROTH's theory it might be noted that BENDA's observed increase in permeability of the barrier between blood

and cerebrospinal fluid during pregnancy is not directly applicable to the barrier between the calvarium and the dura mater.

8 Hyperostosis is elicited by *an endocrinologically determined metabolic disturbance.* It was perhaps this theory that BONNAMOUR and JAMIN had vaguely in mind when examining the endocrine glands in their case. However, the first protagonist of the endocrine theory was, in fact, STEWART (1928) · "The association of this condition (Hfi) with marked obesity in the insane, and especially those of the female sex, seems to be too frequent to be merely accidental when considered in the light of the pathological changes" of the anterior pituitary lobe His microscopical material includes 3 cases of MS, all women above the age of 60. In Case 1 there was a "marked sclerosis, marked deficiency in the chromophil elements and a strangulation of the cells by tissue." In Case 2 the pituitary capsule was thickened, the anterior lobe sclerotic and the cells atrophic ; rather many Ac's. Case 3 resembled the other two from the microscopical point of view. STEWART thus arrived at his endocrine theory on the basis of clinical-anatomical changes as well as of microscopical investigations.

In 1930 MOREL took up this theory and modified it considerably. He now combined his above-described "traction theory" with a

in the anterior lobe it is primarily a question of lesions of a kind often found in old people, lesions that for the rest correspond well with those observed by STEWART. The changes in the posterior lobe are less equivocal: pigmentation, atrophy, calcification. In 4 cases the examination of the "région infundibulo-tubérienne" showed changes of various types such as compression caused by a pituitary tumour, disorders of the secretion and circulation of the cerebrospinal liquor (cystic plexuses, ependymal or subependymal alterations, pineal cyst), disorders of the circulation of the blood, or atherosclerotic changes in the arteries concerned. According to MOREL these changes form the basis of origin of the syndrome. With STEWART and MOREL's opinions VAN BOGAERT (1930) agreed and also SCHIFF and TRELLES (1931). PENDE (1940) also seems to side with these authors when he speaks of a functional alteration in the neurohypophyseal region. It is not clear from his paper whether he has done any histological investigations. ROSSIER and SECRETAN (1940) emphasize that numerous arguments favour an endocrine etiology. The analogies with FS, CS and the "puerperal osteophytes" indicates pituitary disorder. As almost all histological investigations have established that the hypophysis was normal, the last-mentioned authors side with MOREL in declaring there must be a change or a dysfunction of the infundibulo-pituitary system.

In their opinion this is particularly indicated by the changes of the glucose tolerance curves as well as by the specific dynamic effect of proteins, the adiposity, the amenorrhœa, the disturbed sleep and the hypercholesterolæmia. NIEDNER (1943) seems to have been the last to adopt MOREL's views.

In 1938 REIDER made an examination of 1 case of MS with regard to the changes found by MOREL: "The wall of the third ventricle, said by MOREL to be the site of granular degeneration of a type characteristic of Hfi and thought by him to be indicative of derangement of calcium regulating centres, in this case showed no unusual changes. The left frontal lobe showed findings characteristic of Alzheimer's disease."

As early as 1936 we expressed the opinion that MS, and especially Hfi, must be endocrine disorders. The following reasons indicate most definitely that we have here to do with an endocrine, especially a pituitary, disturbance, namely, that Hfi is an almost specifically female anomaly, that it almost only occurs after the menopause, that it resembles the puerperal osteophytes and that it very often is accompanied by constitutional modifications in a masculine direction and with obesity. This theory is further strongly supported by the not uncommonly occurring combination with acromegaloidism or with genuine acromegaly as well as by a habitus which sometimes resembles Cushing's syndrome Our histological investigations in 1937 into the changes in the anterior pituitary lobe did not yield any definite results. At that time we thought that we were able to demonstrate a simultaneous increase in the number of Ac's and Bc's, although we stressed that our investigations "did not as yet permit of any definite conclusions. They indicate very strongly the absolute necessity of an exact quantitative micro-analysis of the human pituitary body." And we maintained elsewhere "that the picture, at least in an ordinary subjective 'estimation' of the quantitative relations between the various cell types, was not pathognomonic"

In 1 case of MS FATTOWICH (1938) observed a "hypophysitis chronica interstitialis productiva," a change which apparently corresponded to that found by STEWART. In a case of pronounced MS, RITTER found a basophil hyperplasia of the anterior pituitary lobe and an extensive hyperplasia of the suprarenal cortex, owing to a superabundant storing mainly of double refracting lipoids. KORPASSY (1938), who made post-mortem examinations of 5 cases of MS, says that the syndrome is indicative of a disturbance of the ovaries and of the pituitary body. The endocrine glands did not show any relevant changes, however, so that further investigations are still necessary.

In 1942-43 MELLGREN carried out careful histological investigations with the aid of modern methods In 5 cases of MS he found a constant increase in the number of hypertrophic amphophil cells in the anterior

pituitary lobe, he observed the simultaneous increase of Ac's and Bc's—which we demonstrated in some cases—in 1 single case only. With ordinary staining *the suprarenal glands* did not present any noticeable changes, not even a definite positive reaction in VINES' sense. When using the ponceau-fuchsin reaction small amounts of red granules appeared in several cases, as VINES has described. MELLGREN connected this with the post-climacteric hirsutism in MS. In his latest work he describes the hypophyseal changes more precisely: "The anterior pituitary lobe shows on the whole the same histological change in Cushing's disease, adrenal virilism, MS, 'Cushingoid habitus' and prostatic hypertrophy, namely, an increase of the number of hyaline basophils and hypertrophic amphophils, together with a less constant relative increase of the number of sparsely granulated basophils. The only difference between the groups in point is that the pituitary change is quantitatively far stronger in Cushing's disease and adrenal virilism than in Syndroma Morgagni, 'Cushingoid habitus,' and prostatic hypertrophy. . . . The observed pituitary change points purely morphologically to a hyperfunction of a definite kind in the Bc's, it being demonstrable that the hypertrophic amphophils are in all probability developed from the basophils. It seems, therefore, likely that the increased number of hyaline basophils and hypertrophic amphophils are the expression of a corticotropic hyperfunction of the anterior pituitary."

FLODERUS (1944) has carried out detailed investigations into the quantitative micromorphological conditions in the pituitary in different pathogenic conditions, among others hypertension and MS. His material of MS is derived from 3 cases, where accurate quantitative determinations, that is, counting of the different cell types, were performed and 4 cases where the quantitative conditions were assessed under the microscope. In some of these cases there was only an Hfi, while hirsutism and obesity were lacking. The results of these investigations do not support our preliminary rather reserved assumption of a simultaneous increase of Ac's and Bc's. It must be borne in mind, however, that FLODERUS' material does not correspond to ours in every respect, as we investigated cases with a complete triad (MS), while FLODERUS had mainly cases of Hfi without any pronounced virilism or obesity. In the case of MS (or, more correctly, Hfi) FLODERUS found no divergences at all from the morphological picture observed in individuals in whom the syndrome (or better, Hfi) was absent. FLODERUS has not made any more detailed examinations of the various cell types, and therefore does not discuss MELLGREN's supposed increase of the hypertrophic amphophils.

As we have seen, MELLGREN and FLODERUS have made important contributions to our knowledge of the cytology of the endocrine organs in MS. The question of the pathogenesis of the "leading" symptom

In their opinion this is particularly indicated by the changes of the glucose tolerance curves as well as by the specific dynamic effect of proteins, the adiposity, the amenorrhœa, the disturbed sleep and the hypercholesterolæmia. NIEDNER (1943) seems to have been the last to adopt MOREL's views.

In 1938 REIDER made an examination of 1 case of MS with regard to the changes found by MOREL: "The wall of the third ventricle, said by MOREL to be the site of granular degeneration of a type characteristic of Hfi and thought by him to be indicative of derangement of calcium regulating centres, in this case showed no unusual changes. The left frontal lobe showed findings characteristic of Alzheimer's disease."

As early as 1936 we expressed the opinion that MS, and especially Hfi, must be endocrine disorders. The following reasons indicate most definitely that we have here to do with an endocrine, especially a pituitary, disturbance, namely, that Hfi is an almost specifically female anomaly, that it almost only occurs after the menopause, that it resembles the puerperal osteophytes and that it very often is accompanied by constitutional modifications in a masculine direction and with obesity. This theory is further strongly supported by the not uncommonly occurring combination with acromegaloidism or with genuine acromegaly as well as by a habitus which sometimes resembles Cushing's syndrome Our histological investigations in 1937 into the changes in the anterior pituitary lobe did not yield any definite results. At that time we thought that we were able to demonstrate a simultaneous increase in the number of Ac's and Bc's, although we stressed that our investigations "did not as yet permit of any definite conclusions. They indicate very strongly the absolute necessity of an exact quantitative micro-analysis of the human pituitary body." And we maintained elsewhere "that the picture, at least in an ordinary subjective 'estimation' of the quantitative relations between the various cell types, was not pathognomonic"

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In 1942-43 MELLGREN carried out careful histological investigations with the aid of modern methods In 5 cases of MS he found a constant increase in the number of hypertrophic amphophil cells in the anterior

Knaggs (1926) apparently possesses a wide experience of the changes in acromegaly. According to him the changes of the calvaria are not nearly so pronounced as those found in the jaw-bones, the supraorbital arch and the facial bones Their thickness varies considerably Most acromegalic skulls are thicker than normal; in some very few cases they are so thick that they resemble the calvaria found in osteitis deformans. In some cases the two tables are clearly outlined, but in others it is impossible to distinguish them from the dense diploe The frontal bone is the first part to be attacked, and undergoes the most extensive changes; in many cases there is a tendency to form small dense osteomata on the inner table.

Cushing and Davidoff (1927)—Case 1 Man, 52 years old. The bones of the skull, particularly the frontal, were greatly thickened; the increase appeared to be confined to the inner table, and rough hyperostoses extended over practically the entire inner surface of the frontal bones The occipital bone was thinner. Testes 74 g., hyperplasia of the interstitial cells Case 2 Man, 40 years old Great increase in thickness and density of the cranial vault, more pronounced in the frontal region. Testes 23 g, highly atrophic and sclerotic Case 3. Man, 36 years old, suffering from diabetes The calvaria was remarkable for its thinness wherein it differed from the usual acromegalic skull There were a few frontal enostoses and the greatest thickness was 6 mm Testes very small, only 2 × 2 5 cm Atrophy and dedifferentiation of the epithelium, excessive interstitial connective tissue, no Leydig's cells. Case 4 Woman, 52 years old Acromegaly; pituitary adenoma Nothing unusual noted regarding the cranium

Greig (1928)—Case 18 Nullipara, 48 years old Acromegaly from the age of 14. The frontal part shows nodular osteophytic growths from each side of the sagittal sulcus to the obliterated coronal suture Anteriorly the

Morel in his work was greatly interested in acromegaly, and compared the changes found in MS with those observed in acromegaly The microscopical pictures of the bones resembled one another, and the localization of the hyperostosis is analogous in certain respects, finally, symptoms of acromegaly and of Hfi were in some cases present simultaneously (cases published by Beadles, Naito and Greig)

In 1936 Moore found three clear-cut examples of acromegaly in Hed (40 cases), and observed further that 17 unmistakable examples of acromegaly did not show any increased thickening of the calvaria. When studying the X-rays from 27 cases of acromegaly he found "that the hypertrophy or overgrowth of bones in that disease was readily distinguished from the changes of hyperostosis"

Troell (1938)—Case 1. Woman, 43 years old Acromegaly and thyrotoxicosis, pituitary adenoma Case 2. Woman, 41 years old, acromegaly and thyrotoxicosis, Hfi, no post-mortem examination

According to Soto (1939) the hyperostoses extend over the whole skull in acromegaly.

Allison, Berthoud and Brantway (1944-45) observed a case of acromegaly combined with Hfi in a woman aged 66, during fourteen years Except headaches there were no symptoms belonging to Morel's syndrome. No autopsy.

within Morgagni's triad, the Hfi, still remains unanswered, however. As the cell changes observed by MELLGREN are to be found in syndromes with Hfi as well as without Hfi, their pathogenetic rôle in Hfi seems at least questionable; that the two other components of the MS are causally closely connected with these changes seems to be proved by MELLGREN'S investigations. FLODERUS was unable to demonstrate any certain divergences from the cytological picture in cases without Hfi. This, too, indicates that *the question of the cytological conditions in the pituitary in cases of Hfi still remains unanswered.*

The theory of the endocrine nature of Hfi receives an additional support from observations often made on acromegalic skulls.

But little attention seems to have been paid to *the changes in the inner table in acromegaly*, although they evidently are by no means rare. As a matter of fact the ordinary textbooks give nothing but vague suggestions. It seems on the whole uncertain whether the conditions are the same in men and women or not.

In MARIE'S classical case, a 54-year-old woman, examined post mortem *by BROCA, the calvaria was thick and spongy. No changes resembling Hfi* were mentioned. The following cases are quoted from the later literature.—

BEADLES (1898)—Woman, 40 years old, with acromegaly and obesity.

thin only at the temples, flat osteophytes on the interior surface of the frontal bone.

REINHARDT and CREUTZFELDT (1913)—Man, 47 years old. Smooth inner surface of the calvaria The inner surface of the frontal bones, especially the right one, is fairly uneven and nodular. The testes are small, atrophic and degenerated.

NAITO'S (1924) 9 cases show the following changes in the frontal bone· Case 4. Man, 43 years old, "hyperostosis principally in the region of the frontal bone" Case 5. Woman, 46 years old, calvaria 12 mm. thick, the *inner surface of*
arterial sulci are
of the frontal bo[illegible]
diploe 8 mm. C[illegible]
as in cases of [illegible]
only a moderate thickening of the calvaria. Among the cases with Hfi he has a further 2 where there is either a pituitary tumour or where such a tumour is suspected. Case 9 Woman, 82 years old, with pituitary tumour (acromegaly) and senile hyperostosis of the frontal bone On the interior surface of the frontal bone "a considerable thickening, in some places amounting to 14 mm Pituitary tumour verified at operation The special interest in this case centres on the combination of a pituitary tumour and frontal enostoses, which mostly or even exclusively are to be regarded as senile phenomena" (NAITO) Case 10 Woman, 59 years old, with "concentric hyperostosis" of the calvaria, frontal hyperostosis and visual disturbance, for which reason a pituitary tumour was suspected X-ray of the pituitary body was normal As further details are lacking, the case seems rather vague.

constant change in acromegaly, or whether there is a more or less accidental combination of acromegaly and Hfi. With regard to his Case 9, NAITO speaks of a "combination of pituitary tumour and frontal enostoses." According to GREIG the connection was mainly accidental: "Acromegaly does not stand to cranial osteophytes as cause and effect." In my opinion it is neither a question of an accidental combination nor of any causal connection in the sense denied by GREIG, but of two phenomena, which resemble each other very much from a morphological and pathogenetic point of view, as acromegaly and Hfi represent two closely related endocrine disorders

During *pregnancy*, too, we may observe changes of the inner table which resemble Hfi more or less, and may even be mistaken for it. These changes are also of great importance in discussing the pathogenesis of Hfi.

Even early authors, *e.g*, HOWSHIP and ROKITANSKY, were well acquainted with the so-called *puerperal osteophytes* In 1884 DUCREST states that this condition occurs in more than 50 per cent. of all pregnant women, and especially at the end of pregnancy. It is more frequent in primiparæ and in young women than in multiparæ and old women. HANAU, who found osteophytes in only 20 to 25 per cent of the pregnant women, performed detailed investigations into their histogenesis and classes them together with the "physiological osteomalacia" which he had observed in pregnant women; in his opinion this osteomalacia is characterized by newly formed non-calcified bone tissue.

RIBBERT has a short reference to the warty protuberances on the interior surface of the skull "during pregnancy and of unknown origin."

In their work on the developmental conditions of the skull, LOESCHKE and WEINNOLDT (1922) discuss the skull thickening during pregnancy, which, like the senile changes, "show pronounced and, as a rule, tent-shaped proliferations of the inner table" As the rest of the skeleton, too, shows such thickenings during pregnancy, these authors assume that the causative factor must be a hormonal stimulus.

DRESSLER discusses the possible connection between puerperal osteophytes and Hfi, and expresses the opinion that the puerperal thickening of the calvaria is likewise mainly mechanically determined. The "hormonal stimuli" suggested by LOESCHKE and WEINNOLDT "probably only lead to disposition of the bone to react strongly to a weak stimulus." His material contains several cases of puerperal osteophytes, which are not, however, interpreted as such.

GREIG (1928) pays considerable attention to the puerperal changes of the inner table, which for the rest show but little resemblance to Hfi, "the nodular variety . . . the whole of the inner table anterior to the coronal suture is covered by a regular fine deposition of new bone, which is whiter and less vascular than the bone it overlies . . . On

We have ourselves observed the cases summarized below :—

Group III, Case 83—Woman, 58 years old. Pronounced acromegaly, hirsutism, obesity, wart-like bony thickenings on the interior surface of the calvaria, most marke [illegible] the occiput (Fig. 4).

Group III, Case 1[illegible] no acromegaly, abundant hirsutism, atypical wart-like thickenings of the inner table, especially in front of the coronal suture. Suprasellar meningoma (Figs. 6, 7 and 8)

Group VI, Case 1—Woman, 40 years old. Increasing acromegaly, pronounced hirsutism, obesity, radiologically typical Hfi (Fig. 9), widening of the sella (13 × 11 mm.).

This short survey of the changes in the calvaria in acromegaly, which has no pretensions to completeness, covers 19 or 20 cases—7 men and 12 or 13 women; there are, further, about 25 to 30 summarily described cases. It is clearly evident that the appearance of the calvaria varies. In many cases there do not seem to be any changes; in others, *e.g., those reported by* MOORE, *a Hcd was observed. Thickening of the* calvaria was also observed in MARIE-BROCA's case, in NAITO's Case 6 and in CUSHING-DAVIDOFF's Case 2. In 5 cases the descriptions do not allow of any certain conclusions, although it seems probable that there may have been an Hfi-like change.

Consequently the most interesting cases are the 14 where an Hfi-like change of the inner surface was observed. At least 9, and perhaps 11, such female cases are reported, as well as at least 5, and perhaps 7, male cases. In 4 of the 7 male cases there is some reference to the state of the testes. REINHARDT-CREUTZFELDT's case showed atrophy and degeneration, CUSHING-DAVIDOFF's Case 1 had an increase in number of the interstitial cells, but no atrophy, their Case 2 had atrophy and sclerosis . and their Case 3 a very pronounced atrophy and degeneration.

The calvarial changes found in acromegaly seem to differ somewhat from a typical Hfi, at least in some of the cases; they are not infrequently described as small nodular or small wart-like, which corresponds well to the findings in our 2 autopsy cases The thickenings are also spread over a greater surface, sometimes over the whole inner surface—which is another difference.

Finally, the relatively great number of male cases 5 and 7 respectively, as against 9 and 11 female cases, is also rather remarkable; this must be viewed in relation to the fact that acromegaly is on the whole slightly more frequent in men.

Nothing very much is known of the microscopical appearance of the inner table in acromegaly According to MOREL the histological picture seems to resemble that found in Hfi, which corresponds well with our own observations in 2 cases

The question now presents itself whether these Hfi-like warts on the inner table are to be interpreted as a characteristic although not

constant change in acromegaly, or whether there is a more or less accidental combination of acromegaly and Hfi. With regard to his Case 9, NAITO speaks of a "combination of pituitary tumour and frontal enostoses." According to GREIG the connection was mainly accidental · "Acromegaly does not stand to cranial osteophytes as cause and effect." In my opinion it is neither a question of an accidental combination nor of any causal connection in the sense denied by GREIG, but of two phenomena, which resemble each other very much from a morphological and pathogenetic point of view, as acromegaly and Hfi represent two closely related endocrine disorders.

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the inner table of the parietals there is a fine, very irregular deposit of new bone arranged in map-like areas." According to Greig the puerperal osteophyte has "a similar origin [as the Hfi] but it is not the nodular variety, it cannot become the nodular variety nor can the nodular variety become the puerperal osteophyte." His work contains a couple of very good macroscopical reproductions. It is not quite clear what Greig means by "similar origin"; he probably wishes to say that the similarity refers to the morphogenesis only.

In a couple of studies (1936, 1937) *we summed up the endocrine* disturbances occurring during pregnancy under the term the "pregnancy syndrome" (PS), and proposed it as the counterpart to MS. Morel (1937) seems to reason along much the same lines when he compares Hfi and the changes connected with it with pregnancy: "The one is progressive, the other passing."

Is Hfi a Separate Morphological and Pathogenetical Entity?

From a systematic point of view it is then only justifiable to ascribe a wider significance to Morgagni's hyperostosis if it is possible distinctly to differentiate this particular type of skull thickening from other types.

Naito (1924) distinguishes between no less than 11 types of hyperostosis.

[illegible] es (hyperostotic tower skull). [illegible] (4) Paget's osteitis deformans. [illegible] osteitis fibrosa (7) Partial skull [illegible]

To this classification, which is mainly an enumeration, Naito adds *a classification from the anatomical point of view—of but little interest* in the present connection—and an etiological classification :—

(*a*) Congenital (hereditary) = Group 1. above (*b*) Mechanical = Group 11 above, thus principally Hfi. (*c*) Circulatory, in cerebral tumour, epilepsy, psychosis, cardiac and vascular diseases (*d*) Inflammatory, especially syphilitic (*e*) Endocrine acromegaly and "possibly Paget's disease" (*f*) Dyscrasic, especially in rachitis (*g*) Neoplastic (osteoma, osteosarcoma, meningoma)

Stewart's *classification (1928) refers only to Hfi and need, therefore*, not be treated here

The works by Moore, already discussed above, are especially important for the study of the present problem. In 1936 he discusses in detail the pathogenesis of the four principal types which he suggested in 1935: "The fact that the hyperostoses coexist in the same persons and that the skulls are generally thickened in cases of all types sustains

the view that, though morphologically distinct, all types have the same fundamental etiology; this is indicated also by the related clinical phenomena." In a second work from 1936 he writes: "The symptom complexes of the several types are closely allied, and in the future they may be proved to be identical . . . all types have the same fundamental etiology."

MOORE's opinion has been adopted by a great number of authors, above all, by CARR and by ROSSIER and SECRETAN.

ROSSIER and SECRETAN "accept MOORE's classification." They dispute as artificial the attempt to separate Hfi from other kinds of skull thickening. They have observed the gradual transformation of the nebula frontalis in Hfi as well as the association of Hfi with Hcd. It therefore seems to them as if the various types might merge into each other. The majority of their cases belonged to the Hfi type.

MONIZ (1938) is not quite convinced by MOORE's unitarian views. It is "probable, but we cannot affirm," that the four types have the same etiology. All these types of hyperostosis must be studied in their clinical and patho-anatomical aspects before one can arrive at any final opinion.

LUCHERINI (1939) on the whole rejects MOORE's theory, and maintains that Hfi should be separated from the group of cranial dysostoses because of its special characteristics (age, frequency, sex, localization, anatomical-radiological appearance and the difference between the endocranial and the endocrine symptoms)

The connection between Hfi and the diffuse hyperostoses of the skull has been discussed recently by OLDBERG (1944) By means of radiological investigations he arrived at the conclusion that Hfi "is positively correlated with a diffuse thickening of the os parietale and consequently with the diffuse thickening of the calvaria" According to OLDBERG "we have to reckon with all types of transition between simple diffuse thickenings and thickenings of a more protruding and circumscribed character." It is therefore also necessary to assume a homologous genesis. In cases of general thickening of the calvaria a hypophyseal origin might "be assumed just as well as in local frontal hyperostosis" We shall return to a more detailed discussion of these questions

Without taking any part in the discussion of MOORE's four types, we have ourselves in 1939 proposed an etiological-morphological classification of the hyperostoses The first group was to contain the compensatory hyperostoses in brain atrophy, the second the dysostotic (rachitis, etc) and inflammatory hyperostoses (lues) as well as those occurring in connection with meningoma, the third and last would contain the dyshormonal hyperostoses (pregnancy, MS, PMS). By means of a clever and easily made modification of our scheme, SZABLOCS arrived at the following classification of skull hyperostoses:

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[illegible] (d) Mechanical = Group I [illegible] *ar, epilepsy,* [illegible], especially syphilitic. (*e*) Endocrine acromegaly and "possibly Paget's disease" (*f*) Dyscrasic, especially in rachitis (*g*) Neoplastic (osteoma, osteosarcoma, meningoma)

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of the skull, and consequently also the difficulties connected with the present problem, we have examined 40 skulls from women in the ages between 44 and 89 years Figs. 59 to 98 show transverse sections of about the same thickness (6 to 7 mm.) through the left tuber frontale. The great variation as regards thickness and density is well apparent in the figures Within each age group there are thick and thin, sclerotic and porous skulls. It is further evident that the thickness in the sagittal plane and its immediate surroundings does in no way always correspond to the thickness of the rest of the parietal bones. Several skulls, e g., Nos 62, 67, 68, 78, 83, 88, 91, 93 and 98, are thicker in the sagittal plane than elsewhere; other skulls are thinner in the sagittal plane than over the tuber parietale (Nos. 64, 72 and 85).

We also examined the correlation of Hfi to the thickness of the parietal bones. The average thickness of the bone was denoted by Figs 1 (thin), 2 (moderate), 3 (slightly thickened) and 4 (greatly thickened), and the degree of Hfi expressed as usual The results of this investigation are seen in the table —

TABLE 27

Hfi	Average Thickness				Total
	1	2	3	4	
0 . .	6	5	3	1	15
(+) . .	1	3	3	2	9
+ .	0	4	4	1	9
+ +	1	2	1	1	5
+ + + .	0	0	1	1	2
Total	8	14	12	6	40

Among the 24 skulls without any Hfi or with only a trace of Hfi there were thus 15 thin or moderately thick and 9 more or less thickened skulls. Among the 9 skulls with Hfi +, 4 were moderately thick and 5 thickened. Among the 7 skulls with pronounced or very pronounced Hfi (+ + or + + +), 3 were thin or moderately thick and 4 definitely thickened. The early experience that Hfi is not uncommonly connected with thickening of the skull is thus confirmed, at any rate if the parietal bone is permitted to represent the whole skull.

3. Between the two morphologically well-defined changes of the skull which we call Hfi and diffuse hyperostosis respectively, we find combinations that might be interpreted as transitions, especially in the lateral X-ray of the frontal bone. An Hfi may develop in a woman with Hcd or Hfp if the etiological factor in question asserts itself, and in the same way an Hcd or Hfp may develop in a woman with Hfi

(1) Compensatory, (2) hormonal, (3) dysostotic, (4) irritative hyperostoses. On the basis of this classification LESZLER (1940) published a general survey of the radiology of skull hyperostoses.

Against the opinion held by MOORE and others, viz., that the different types of hyperostosis have the same fundamental etiology and in the future may be proved to be identical, the following arguments might be advanced.

1. A comparison between the frequency of diffuse hyperostoses and Hfi in the two sexes does not support the unitarian opinion. Diffuse skull thickenings occur in both sexes, but are, as has been long known and is, indeed, borne out by our own experience, more common in women than in men. According to MORTIMER, 63 per cent. of 494 dysplastic skulls were found to occur in women and 37 per cent. in men. On the other hand the frequency of Hfi is, according to our series, about a hundred times as high in women as in men. If the diffuse hyperostoses and Hfi were identical from an etiological point of view, as MOORE and others believe, the same relative frequency of the two types of skull changes ought to be expected in the two sexes. This is not at all the case, however

2. The two principal types of skull thickening, the more diffuse one (Hed and Hfp) and Hfi, do not always occur simultaneously; each of them may occur separately. In this connection it is important to remember that Hfi—as we have shown above, and as MOORE, too, concedes—may appear also in otherwise thin skulls (Figs. 1, 12 and 35).

As mentioned above, OLDBERG has made an attempt with the aid of X-ray pictures to demonstrate statistically a positive correlation between Hfi and diffuse hyperostosis. This question is very complicated and difficult to solve, however. We are ourselves of the opinion that it is not suitable for statistical studies as it is only in some few cases that the thickness of the skull can be expressed in simple terms like thin, medium and thick, or by seemingly exact figures. The thickness of the individual skull often shows too great local variations for such a nomenclature. It does not further seem possible to consider the radiological profile of the skull to be decisive, as the thickness of the skull in the immediate proximity of the sagittal sinus is in no way [illegible] representative of the skull as a whole. Further, Hfp frequently [illegible] listinctly on a lateral picture Not even [illegible] ıria uniformly sawn can always be considered representative, as, besides thin and thick skulls, there are to be found also porous and compact ones. A thick skull is consequently not always heavy For the rest, an anatomical series would be more suited for statistical studies of the correlation between Hfi and the diffuse hyperostoses, but even then there must be exact definitions of what the terms thin or thick skulls really are intended to mean.

So as to demonstrate the great variations in thickness and density

of the skull, and consequently also the difficulties connected with the present problem, we have examined 40 skulls from women in the ages between 44 and 89 years. Figs 59 to 98 show transverse sections of about the same thickness (6 to 7 mm) through the left tuber frontale The great variation as regards thickness and density is well apparent in the figures Within each age group there are thick and thin, sclerotic and porous skulls. It is further evident that the thickness in the sagittal plane and its immediate surroundings does in no way always correspond to the thickness of the rest of the parietal bones. Several skulls, *e g.*, Nos 62, 67, 68, 78, 83, 88, 91, 93 and 98, are thicker in the sagittal plane than elsewhere; other skulls are thinner in the sagittal plane than over the tuber parietale (Nos. 64, 72 and 85).

We also examined the correlation of Hfi to the thickness of the parietal bones The average thickness of the bone was denoted by Figs. 1 (thin), 2 (moderate), 3 (slightly thickened) and 4 (greatly thickened), and the degree of Hfi expressed as usual The results of this investigation are seen in the table :—

TABLE 27

Hfi	Average Thickness				Total
	1	2	3	4	
0 . .	6	5	3	1	15
(+) . .	1	3	3	2	9
+ . .	0	4	4	1	9
+ + .	1	2	1	1	5
+ + +	0	0	1	1	2
Total	8	14	12	6	40

Among the 24 skulls without any Hfi or with only a trace of Hfi there were thus 15 thin or moderately thick and 9 more or less thickened skulls Among the 9 skulls with Hfi +, 4 were moderately thick and 5 thickened. Among the 7 skulls with pronounced or very pronounced Hfi (+ + or + + +), 3 were thin or moderately thick and 4 definitely thickened The early experience that Hfi is not uncommonly connected with thickening of the skull is thus confirmed, at any rate if the parietal bone is permitted to represent the whole skull.

3. Between the two morphologically well-defined changes of the skull which we call Hfi and diffuse hyperostosis respectively, we find combinations that might be interpreted as transitions, especially in the lateral X-ray of the frontal bone. An Hfi may develop in a woman with Hcd or Hfp if the etiological factor in question asserts itself, and in the same way an Hcd or Hfp may develop in a woman with Hfi

if the pre-requisite etiological conditions are at hand. Conclusions as to the etiology must always be drawn with the greatest care from the morphological findings. Even when there are great morphological differences the etiology might be identical. On the other hand, the simultaneous occurrence of two etiologically well-differentiated but *morphologically similar changes within one organ is not very uncommon.* As is well known, it took quite a long time before luetic aortitis came to be separated from the often simultaneously occurring atherosclerosis.

4. Much of our knowledge regarding the skull changes in senile atrophy of the brain is also against MOORE's unitarian views. As has been shown above, although Hfi has nothing to do with senile atrophy of the brain, yet, on the other hand, senile atrophy of the brain evokes a considerable new formation of bone on the inner surface of the skull which may in its turn cause a thickening of the skull if there is no *corresponding resorption of bone from the outer surface.* The importance of endocrine factors in diffuse skull thickenings is therefore not relegated to the background, as such factors are very important, especially in acromegaly.

5. In support of their unitarian opinion, MOORE and others also cite the supposed clinical symptoms which are said to be identical. The fact that patients with Hfi and patients with Hcd or Hfp show on the whole the same clinical symptoms is in itself scarcely surprising, as both Hfi and Hcd or Hfp occur principally in elderly women and as, furthermore, both groups of skull changes are not infrequently connected. Again, subjective symptoms, commonly occurring in elderly women, may have caused the patients to present themselves for radiological examination.

For various reasons we therefore arrive at the conclusion that from a pathogenetic point of view Hfi must be distinguished from Hcd and Hfp. Hfi is mainly or purely an endocrine condition, the diffuse skull changes are both mechanically — through the atrophy of the brain — and endocrinically determined Hfi must therefore be considered to hold a unique position both morphologically and etiologically. Among the other changes of the inner surface of the skull it is the *acromegalic* ones that are most closely related to Hfi, in this case the combination with a diffuse thickening of the skull seems actually to be the rule.

In the present connection it is scarcely necessary to discuss further the *relations of Hfi to puerperal osteophytes* They are easily separated both morphologically and pathogenetically, but are nevertheless closely related to each other The puerperal change is a passing and the Hfi a more permanent one, and they are only exceptionally found together. Hfi may develop in a nullipara just as well as in a multipara.

CHAPTER SIX

MORGAGNI'S TRIAD AS AN ENDOCRINE SYNDROME

A comparison with certain other polyglandular or hypophyseal syndromes is particularly instructive in trying to understand MS. From the long list of endocrine syndromes we have chosen five and arranged them in Table 28, where the "key position of the hypophysis" stands out very clearly: (1) *The pregnancy syndrome,* (2) *Morgagni's syndrome,* (3) *Pierre Marie's syndrome (acromegaly),* (4) *Cushing's syndrome,* and (5) *Fröhlich's syndrome (the adiposo-genital dystrophy).*

TABLE 28

	Skeletal Changes	Increase of Soft Tissues	Hirsutism of the Face	Hairless Axillæ and Pubes	Obesity	Hypogenitalism
Pregnancy syndrome F	Cranial osteophyte, etc	+	(+)	.	(+)	+
Morgagni's syndrome F (and M)	Hfi (osteoporosis)	+	+ +	(+)	+ +	+
Pierre Marie's syndrome acromegaly M and F	Cranial hyperostosis (osteoporosis)	+ +	(F+)		(+)	+
Cushing's syndrome F (and M)	Osteoporosis	?	F + +	(+)	+ +	+
Fröhlich's syndrome M (and F)	?	. .	M –	+	+ +	+

1. The Pregnancy Syndrome (PS) (Henschen, 1936)—Since 1936 we have collected the more or less pronounced endocrine disturbances
' pregnancy
but poorly

To the PS belong first of all *disturbances of the bone system.* The puerperal osteophytes which are said to be radiologically demonstrable in about one-third of all pregnant women (Dreyfus) are certainly extremely frequent in their less developed forms. We have ourselves constantly observed this change, or at least traces of it, at post-mortem examinations of pregnant women in the eighth and ninth months. As

showing no similarity at all, have been described in detail above. For the rest, the periosteal thickenings during pregnancy are not limited to the inner surface of the skull but are to be found on the facial bones

and the bones of the trunk and the extremities, and contribute together with a hyperplasia of the soft tissues to the well-known and often disfiguring coarseness and increase in size of these parts. According to ERDHEIM the cartilage also is engaged in the hyperplasia.

It seems fairly certain that the soft parts and the internal organs also share in the same process, and it seems equally justifiable to assume that the increase in weight of the organs and the whole body, observed by AGDUHR in experimental animals after pregnancy, is to be found in women too.

Greater degrees of bone thickening and hyperplasia of the soft parts cause symptoms that are known under the term *pregnancy acromegaloidism*. It is here evidently a question of a constitutional disposition, as cases are known where the woman at each pregnancy goes through the same coarsening process, which disappears after parturition. In rare cases a real acromegaly may develop, as in FRUHINSHOLZ'S, MAREK'S and KEHRER'S cases.

In MAREK'S case the acromegaly set in during the eighth month and disappeared spontaneously seven weeks after parturition.

KEHRER'S *case was a 30-year-old woman who showed obesity* and [illegible]. The [illegible] there [illegible] no disturbances at all during her fourth pregnancy. An examination during her fifth showed a very tall woman with a strong suspicion of acromegaly, extreme general adiposity, probably of diencephalo-hypophyseal type, diffuse [illegible] diabetes. The [illegible] cal examination [illegible], however, does not exclude the presence of pituitary changes

More frequent than these pronounced changes are, as we know, *disturbances in the fat metabolism* with increased accumulation of fat, which at times may attain pathological dimensions.

Many women develop a *polyuria* at the end of the pregnancy. FORSSMAN has recently studied the pregnant women in a family with hereditary diabetes insipidus where the operative gene is linked to the sex chromosome He was here able to demonstrate that the otherwise latent gene became manifest in some of the pregnant women and brought about a diabetes insipidus gravidarum.

Disturbances in the growth of hair are also known, especially in the form of the so-called pregnancy hypertrichosis (BORCHARDT).

The mental disturbances observed in many pregnant women, which are partly endocrinically determined, can be left out in this connection.

Our knowledge of the *changes in the endocrine organs* in these metabolic disturbances in the pregnant woman is as yet very incomplete. Neither the anatomical nor the functional basis has even begun to be investigated, especially in relation to the complicated changes of the

pituitary body. "The doctrine of the pituitary disturbances during pregnancy still remains vague and unsatisfactory in several respects" (GUGGISBERG, 1936)

An enlargement of the anterior pituitary lobe with tumour symptoms such as disturbed vision and bitemporal hemianopsy, receding after parturition, has been observed, but up to the present the microscopical picture, however, has not been described in detail. Ac's apparently occur besides the pregnancy cells in acromegaly, and Bc's in adiposity, although no certain information on this point is to be found in the available literature.

2. Morgagni's Syndrome (MS) (HENSCHEN, 1936)—There is a striking resemblance between the PS of the young woman and the MS of the post-climacteric woman. MS might even be called the PS of the old woman. Both syndromes are only slightly pathological, and it is only in exceptional cases that we might speak of a disease in the clinical sense.

Skeleton—Hfi corresponds to the puerperal osteophyte, and, as we know, sometimes extends over large areas of the inner surface of the skull. Unfortunately the condition of the rest of the skeleton in MS is only partially investigated, but we may assume that other periosteal thickenings may be present, as well as the enlargement of the atlas, recently demonstrated by OLDBERG, which favours such an assumption. The coarsening of the face, which often gives a masculine appearance to the old woman, as well as the enlargement of the hands and feet, sometimes observed in connection with Hfi point to not only a periosteal but also a general proliferation of the tissues, involving the soft parts as well Our own material contains a number of cases where we must speak of a true *acromegaloidism*. The combination with genuine acromegaly is known already in the literature and we ourselves have some verified cases, which are summarized on page 146.

The general osteoporosis, which not infrequently occurs in MS, is of great interest, as it is reminiscent of similar, long-recognized changes in PMS and CS, and as it throws some light on the close relationship between the three syndromes.

The tendency to accumulation of fat, not uncommonly observed in pregnancy, increases in MS and becomes a pronounced, often extreme, obesity, recalling that of CS and FS.

The male growth of hair in the face, "le virilisme pilaire" of the French, which does not play any very great rôle in the endocrine disturbances during pregnancy, plays a much greater one in MS, though not comparable with that observed in CS

Hirsutism is, on the whole, a very frequently occurring anomaly in women, and can be observed in various conditions. The vast literature connected with this matter cannot be discussed here, and we only wish to mention the so-called *syndrome d'Apert*, which is

characterized by changes having much in common with Stewart-Morel's syndrome and with MS in the sense which we have suggested: "Virilisme pilaire, adiposité et troubles du développement corporel, troubles génitaux, évolution maligne avec phase d'hypersthénie, puis d'asthénie terminale." From the patho-anatomical point of view the *syndrome is said to be characterized by hyperplasia or neoplasia of* the suprarenal cortex and by atrophy of the ovary. Interesting data regarding anomalous growth of hair are found in Koechlin's thesis, "Le virilisme pilaire chez la femme" (1921), and in Minet's and Houcke's works (1935). We know less about the hypertrichosis in acromegaly, discussed below, and especially in adipose-genital dystrophy, which is, however, rarely met with in women.

The falling out of the axillary and pubic hair, not infrequently observed in our cases of MS, is such a common change in old and very old women that it need only be mentioned very briefly. It recalls the conditions in Simmond's and Fröhlich's syndromes.

The *hypertension* often found in MS has also its counterpart in CS. Disturbances of the carbohydrate metabolism do not seem to occur as frequently as in acromegaly or in CS.

The polydipsia and polyuria sometimes observed in MS recalls the polyuria not infrequently present in PS, where it may become aggravated and develop into diabetes insipidus.

With respect to the *anatomical changes of the endocrine organs in MS* we should *a priori* expect that a symptom complex which has, as it were, borrowed its components from two other already fairly well-known syndromes—Pierre Marie's and Cushing's—periosteal thickenings and enlargement of the soft parts from the one, obesity and hirsutism from the other—might also present correspondingly combined changes in the endocrine organs, particularly the pituitary body. Future investigations must decide if this really is the case. We once believed that it was possible to demonstrate that Ac's and Bc's, at times presenting an almost adenoma-like appearance, dominated the histological picture of the anterior pituitary lobe. However, it has already been mentioned that the picture is not pathognomonic, at least not as given by an ordinary subjective "estimation" of the numerical proportions between the various cell types.

Recent investigations by Mellgren, comprising rather few cases, it is true, emphasize *mainly the presence of an increase of the number* of hyaline basophils and hypertrophic amphophils, together with a less constant increase of the number of sparsely granulated Bc's. Floderus was unable to show any definite deviations from normal in the cases which he examined.

Mellgren found a faint ponceau-fuchsin reaction in the adrenal cortex in certain patients with post-climacteric anomalies of habitus and considered this reaction to be characteristic.

At the present moment it is scarcely possible to make any general pronouncement on the histological picture of the pituitary body in men with MS, as the cases here described seem to be the first to be subjected to microscopical analysis. The *atrophy and sclerosis of the testes*, corresponding to the post-climacteric atrophy of the ovaries in women, which we have found in many cases, is of fundamental interest.

3. Pierre Marie's Syndrome, Acromegaly (PMS)—Acromegaly, supposed to occur about as often in men as in women, has several interesting points in common with MS. In rare cases the change may be observed as early as puberty (puberty acromegaloidism, BRISSAUD and MEIGE, STICKER, J. BAUER). MORTIMER'S case mentioned above comes, perhaps, also under the present heading The pregnancy acromegaloidism has already been discussed A senile type of acromegaly (MODENA) is also said to occur, characterized by an extremely slow development and without any cerebral or other similar functional disturbances, but accompanied by especially pronounced facial changes; this type is of particular interest in the present connection. The pathogenetic correlation between atrophy of the sexual glands and acromegaly seems to be especially marked in women. PUTNAM and DAVIDOFF observed complete amenorrhœa in 73 per cent. and diminished libido in 38 per cent. of their cases. That acromegaly does not always imply the extinction of the woman's genital function is demonstrated, *e g.*, by our Case 83, reported on page 37.

The anatomical and radiological investigations into the appearance of the acromegalic skull are numerous. It is also generally known that the face of the acromegalic woman often assumes a masculine appearance. It is difficult to say whether the acromegalic female skull differs from the male in other respects, however. Data regarding the occurrence of endocranial bone thickenings and a possible Hfi in acromegaly are unfortunately very rare, in older textbooks, *e g*, NOTHNAGEL and KRAUS-BRUGSCH, there are none at all. A survey of the recent literature in this field gives the impression that Hfi and similar changes occur principally in acromegalic women (p. 146).

The atypical cases where acromegaly is combined with hirsutism or obesity are very interesting. These combinations, too, are highly reminiscent of MS.

Cases of acromegaly with "virilisme pilaire" are described by HOHENEGG (35-year-old woman) and VON EXNER (34-year-old woman). SICARD'S and REILLY'S case (30-year-old woman) showed acromegaly, hirsutism and obesity, together with a radiologically normal sella.

Much has been written on the combination of acromegaly and adiposity (LUCIEN-PARISOT-RICHARD, LANGE, and others) Acromegaly can also be accompanied by a pronounced adipose-genital dystrophy or by diabetes insipidus (BORCHARDT). In their series of acromegalic cases PUTNAM and DAVIDOFF found disturbances of the menstrual

cycle in 87 per cent., hypertrichosis in 53 per cent. and glycosuria in 25 per cent. We observed a pronounced hirsutism in a case of acromegaly with Hfi (Group VI, Case 1, p. 41). Diabetes insipidus occurs infrequently.

We do not intend to discuss in detail the *anatomical changes of the endocrine organs*, in particular the pituitary, in PMS. In this connection we wish to point out, however, that they are not in the least so simple and so easily classifiable as they are often alleged to be. Especial regard ought to be paid to all cases of acromegaly without Ac tumour in the anterior pituitary lobe (*e.g.*, our case, p. 37).

Several authors (BERNHARD, MORTIMER and others) have discussed the question of an acromegaly, determined by the central nervous system.

4. Cushing's Syndrome (CS)—Cushing's syndrome, like Morgagni's, occurs nearly exclusively in women. Other common traits are the hirsutism, perhaps especially marked in CS, the adiposity, here said to be of a special type, the hypertension and the hypogenitalism. Disturbances of the carbohydrate metabolism are not infrequent.

The osteoporosis, characteristic of CS, is also fairly frequent in MS, as well as the hypertension and presumably also the hypercholesterolæmia. Diabetes insipidus occurs in rare cases. The great difference between MS and CS lies primarily in the fact that Hfi is said to be absent in CS. As early as 1937 we emphasized this close relationship between the two syndromes, together with a brief remark on the possibility of mistaking an MS for a CS if no radiological examinations were forthcoming.

This is not the place for a closer discussion of the pathological anatomy of CS, for we are here principally interested in the occurrence of Bc's in the anterior pituitary lobe, as a basophilia is very often met with.

The literature from the last ten years tends to show that obesity often is connected with an increase of the Bc's.

TEEL (1931) examined a 20-year-old woman with increasing obesity and abnormal hairiness (growth of hair on the upper lip, the chin, the breast and the extremities). A nodular, 2 5 mm large, accumulation of Bc's on the inferior lateral border of the anterior pituitary lobe was demonstrated microscopically.

In 81 per cent. of his series on obesity (32 cases) ZEYNEK (1933) found an absolute increase of the Bc's He is of the opinion that Bc's have a definite relation to fat metabolism Basophilia was lacking in 6 cases with less-marked adiposity.

RUTISHAUSER (1933) observed a marked increase of Bc's in 3 cases of obesity and osteoporosis (so-called osteoporotic obesity)

BERBLINGER, who published a typical case of Cushing's syndrome, asserts that in Bc proliferation, either in the form of an adenomatous

or a diffuse cell mass, "there is a primary pathological process which by way of the adrenal elicits phenomena belonging to interrenalism."

These observations agree very well with our own, as we have been able to demonstrate a very pronounced basophilia in a great number of fat old women with or without frontal hyperostosis.

This does not definitely decide the rôle played by the basophilia, however, as KRAUS (1935) points out; it is quite possible that the basophilia can more correctly be interpreted as a secondary change of compensatory nature. KONSCHEGG (1935), too, argues on much the same lines.

How complicated the question really is, and how necessary it is to attack the problems concerned with new histological methods, is clearly shown in the works of GELLERSTEDT, GELLERSTEDT and LUNDQUIST, MELLGREN and others on CS, interrenalism and other post-climacteric habitus anomalies.

5. Fröhlich's Syndrome, Dystrophia Adiposogenitalis (FS)—Adipose-genital dystrophy might seem to occupy a position beside the syndromes recorded in the table on page 153 but, on the other hand, the relations of this syndrome to those discussed above are in certain cases quite evident. Disturbances of the fat metabolism, diabetes insipidus, anomalous growth of hair—for example, certain cases of hirsutism in women—and hypogenitalism are, in fact, symptoms that have been observed with all the other types of pituitary disturbances recorded in the table. The frequent loss of axillary and pubic hair in dystrophia adiposogenitalis reminds us of similar changes in many old women with or without MS.

Especially interesting are cases of simultaneous FS and Hfi. ABELY and DELMOND have described an example of this combination.

Typical morphological changes of the pituitary body seem to be lacking in FS In many cases an injury to the anterior lobe by means of tumours of the most varied kind plays a decisive rôle, but, on the other hand, the syndrome is said to occur also when the pituitary is microscopically intact. According to KRAUS, "we are as yet scarcely justified when speaking of the pathogenesis of adipose-genital dystrophy in saying more than that any severe injury to the pituitary-midbrain system—in many respects to be regarded as a functional unit—may elicit dystrophy, and that it seems to be primarily a question of disturbed co-operation between the anterior pituitary lobe and the midbrain"

The preceding discussion illustrates very clearly how close and yet manifold are the relations which connect MS with the other four pituitary syndromes in our scheme The admission of this new syndrome into the

circle of those known of old, apparently throws some light on the interdependence of the various syndromes.

As a matter of fact the pituitary syndromes are so interwoven both clinically and from the point of view of both pathological physiology and pathological anatomy that it is no longer possible to maintain the old classification with its numerous endocrine "diseases." For this reason we have consistently spoken of "syndromes" and not of "diseases." The hypophyseal-polyglandular disturbances form a group now apparently more limited, now apparently more open, within which the plus and minus variants dominating the individual case determine the clinical and symptomatological picture.

In many cases the disturbances appear in the shape of constitutional, often familial, deviations from normal, although without any distinctly pathological traits. In other cases the disturbances of the hormonal equilibrium are so pronounced that the symptom complex is better considered pathological.

MS might be cited as a typical instance of such disturbance. In the great majority of cases it is here a question of a *distinctly anomalous although not very strongly pathologically accentuated variant of the endocrine state of the woman after the climacteric. In our opinion definite clinical symptoms need not necessarily be present.*

Frontal hyperostosis develops too insidiously to elicit any cerebral symptoms , there are perhaps mental deviations from normal, induced by the somatic virilism—hirsutism and coarsening of the features—and certainly the obesity makes greater demands on the circulatory organs, which together with the often present hypertension may be responsible for a number of subjective symptoms and for many of the very frequent organic cerebral changes—with or without clinical symptoms.

The array of mental, neurological and somatic symptoms which constitute an integral part of Stewart-Morel's syndrome ("syndrome de l'hyperostose frontale interne avec adipose et troubles cérébraux") are, however, on the whole but loosely connected with the genuine disturbances observed in women with MS, and are partly of a general senile nature. In this connection we should like to put especial stress on the fact that changes in the brain and the pituitary incident to old age play a not unimportant rôle in the production of symptoms.

The combination of MS with other endocrine disturbances such as polydipsia, polyuria, diabetes insipidus and diabetes mellitus is also rather interesting. A certain biological connection between Morgagni's syndrome and various other mental and physical disturbances is consequently not to be denied. As a matter of fact the great variability of these disturbances makes the biological homogeneity of the actual syndrome and the close interrelationship of the component parts of the triad stand out all the better.

It is not difficult to think of various ways along which *a more detailed investigation into Hfi, MS* and their relations to other pituitary disturbances could be carried out.

In the first place an *exact quantitative microscopical analysis* of the different cell elements in the pituitary body would be most desirable. The importance of exact figures instead of more or less subjective "estimations" when determining the mutual proportions of the elements in the anterior pituitary lobe is patently obvious. On our suggestion FLODERUS has undertaken an arduous investigation of this subject, which is intended to form the basis of further studies.

A *more exact qualitative analysis* of the different cell types is also imperative. Anyone who has occupied himself a little with the cytology of the anterior pituitary lobe is well aware of the insufficiency of the rough classification of the cells into Cc's, Ac's and Bc's In this particular field GELLERSTEDT and MELLGREN have carried out important investigations which still remain to be finished.

Another investigation which ought also to be done is an examination of the *parts of the brain which are, anatomically and functionally, closely connected with the pituitary body.* If the investigation into the parts surrounding the III-ventricle, begun by MOREL and continued by us, has yielded but little decisive information, this might perhaps be due to the fact that they are as yet merely introductory studies.

Apart from these, other morphological approaches are still open. The *pituitary hormones* in women with radiologically diagnosed Hfi, possibly also with a complete Morgagni's triad, ought to be estimated in comparison with negative control cases and with cases with other syndromes of hypophyseal nature The only attempt in this direction —for which we are indebted to Dr E WASSÉN—did not give any conclusive results, but LUFT'S study of the conditions in hirsutism and CS shows that positive results are to be expected.

Hfi and MS as Genetically Determined Phenomena

A Contribution to the Constitutional Pathology

As early as 1927 DRESSLER discussed briefly the possibility that we might here have to do with a hereditary predisposition. He knew nothing of the heredity or accumulated occurrence of Hfi among siblings, however, and asserted on the basis of his mechanistic conception of the genesis of Hfi that "the assumption of special hereditary factors were superfluous."

In the first report on our investigations of MS (1936), and knowing nothing of DRESSLER'S work, we discussed the possibility "that frontal hyperostosis may point to the presence of a latent hormonally con-[illegible]ned gene, bound to the frontal bone, and possibly occurring only

in certain individuals." *On account of scarcity of material we were then unable to demonstrate the familial occurrence of Hfi.*

Owing to lack of material MOORE (1936) was also unable to prove the existence of a genetic factor: "There is no evidence of racial selection and a familial factor is yet to be found." The missing cases were soon obtained. In 1937 DONINI describes a 55-year-old woman with Hfi and adiposity whose senile and demented mother also had an Hfi. This seems to be the *first case in the literature of familially occurring Hfi. In 1940 HEMPHILL and STENGEL observed 3 cases—a 65-year-old mother with an Hfi verified by autopsy*; a 32-year-old daughter, and her daughter, both of them with radiologically diagnosed Hfi—and wrote: "We feel that it suggests that in our cases heredity is an important factor in the production of the hyperostoses, which appear to be the expression of a dominant gene in this family."

In BAUER's opinion MS seems to be rather a more or less typical combination of genes than an interesting endocrine syndrome. He criticizes "those authors who try to explain MS as a pituitary or polyglandular *disorder. An association of several abnormal genes seems far more probable*," he continues, "*as I have occasionally met frontal hyperostosis as a constitutional abnormality without any other* pathological condition." In our opinion it is neither necessary nor justifiable to discuss whether MS is an endocrine or a constitutional anomaly, as MS, like many other constitutional characteristics, develops by means of anomalous hormonal mechanism We may assume that the complex of genetically determined anomalies, which we call MS—*i.e.*, Hfi, virilism and obesity—does not derive from a direct genetic influence on the frontal bone, the growth of the hair or the fatty tissue, but instead from the agency of the endocrine glands or of the factors *which determine the bone formation of the dura, the growth of the facial hair and the fat metabolism It is hardly possible to over-estimate the rôle played by the endocrine factors in the development of normal and abnormal constitutional types MS can no doubt be* considered as a constitutional anomaly which may, as we have stressed repeatedly, occur "*without any other pathological conditions*" *In* this respect we agree completely with BAUER.

A further contribution to the question of the heredity of Hfi was given by KNIES and LE FEVER, who reported no less than 4 cases of Hfi—it is true, diagnosed only radiologically—a 41-year-old mother with two sons, 19 and 13 years old respectively, and one 16-year-old daughter. These cases are exceedingly interesting from a genetic point of view, if indeed an Hfi was really present in these young individuals.

MELLGREN, who in 1942 concentrated mainly on the study of the pituitary, is perfectly justified in characterizing MS as a habitus anomaly, *but when he uses the* adjective "post-climacteric," we

cannot agree with him, for MS, as we know, may occur also before the climacteric, and in men.

Following CAMPOS, SAMSON, CARON and MARTIN (1942) stressed the familial character of MS. CAMPOS (1943) purports to have demonstrated radiologically two instances of a familial occurrence of MS. The first concerned an 80-year-old very fat woman, with Hfi and hypertension, and two of her four daughters, 49 and 48 years old respectively, and both of them very fat; the second, a 64-year-old fat woman and her 39-year-old very fat daughter (who in her turn had a very fat daughter). GROLLMAN and ROUSSEAU, too, attach great importance to the familial occurrence of the skull changes.

Though not all the cases quoted here may be conclusive, it seems to be demonstrated, however, that Hfi and MS, like certain other constitutional anomalies, may occur familially. Our assumption in 1936 that we have here to do with genetically determined deviations from normal thus seems by now to be very well supported.

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A further contribution to the question of the heredity of *Hfi* was given by KNIES and LE FEVER, who reported no *less than 4 cases of Hfi—it is true, diagnosed only radiologically—a 41-year-old mother with two sons, 19 and 13 years old respectively,* and one 16-year-old daughter. These cases are exceedingly interesting from a genetic point of view, if indeed an Hfi was really present in these young individuals.

MELLGREN, who in 1942 concentrated mainly on the study of the pituitary, is perfectly justified in characterizing MS as a *habitus* anomaly, but when he uses the adjective "*post-climacteric*," we

collections of Europe which might be still better classified by being examined in the light of our present knowledge of the frequency and significance of Hfi. To quote but a single instance: in Skenninge, a little old town in the middle of Sweden, a great number of nuns' skeletons have been found in the ruins of the former convent, belonging to the Order of St Birgitta, the skulls of which skeletons are rather interesting from the present point of view.

The method devised by WAGNER (Oslo) seems to be very suitable for the exact determination of the interior dimensions of the cranium.

CHAPTER SEVEN

THE SIGNIFICANCE OF HFI IN PALEOPATHOLOGY

It is not solely from an endocrinological point of view that Hfi attracts our interest. Together with many other normal and pathological bone changes whose character and incidence are known to us, frontal hyperostosis will assuredly become both interesting and important in the determination of skull fragments from recent or ancient times, that is to say, in the domains of *forensic medicine* and *paleopathology*.

Frontal hyperostosis occurs, as we have shown above, almost exclusively in women after the forty-seventh to fiftieth year of life, to a maximum frequency of about 50 per cent. We may thus, in fact, ascribe to frontal hyperostosis the value of a so-to-speak *inconstant sex characteristic*. It is therefore quite conceivable that Hfi might be used in the determination of the age and sex of otherwise almost unidentifiable skull fragments.

It is now about forty years ago since such a case of frontal hyperostosis in a woman from the Norwegian Iron Age aroused a lively interest on account of the curious circumstances connected with the finding.

At the excavation of the famous Viking ship in Oseberg (1904)—nowadays perhaps the most interesting sight in Oslo—the burial mound was found to have been meddled with. Robbers had plundered the sepulchral chamber and taken the jewels from the dead. The skeletal parts were therefore lying in a heap, and several bones and pieces of bone were missing It soon became clear that the grave had contained the bodies of two women. The anatomist GULDBERG estimated the age of one of them at 50 years. SCHREINER, who subjected the skeletons to a second examination, put the age of the same skeleton " not far above 50 years, perhaps 60 to 70, and estimated the age of the other woman at " about 30 to 40 years."

The skeleton of the older woman showed a pronounced arthrosis deformans and a less severe spondylarthrosis anchylopoetica The skull further showed a marked typical frontal hyperostosis (Fig 99), which gave rise to a long discussion in the Medical Association in Oslo as early as 1907. This cranial change, the type and occurrence of which were completely unknown at that time, is, in fact, an additional argument in favour of SCHREINER's opinion, viz , that one of the skeletons from the Oseberg ship once belonged to a woman " not far above 50 years, perhaps 60 to 70 years."

There are numerous skulls in the anthropological and historical

8. The morphological changes of the endocrine organs which form the basis of Morgagni's triad are as yet but imperfectly known. Besides changes in the anterior pituitary lobe there are probably also changes in the suprarenal cortex. The ovaries and testicles are generally markedly atrophic and sclerotic. Whether any characteristic changes take place in the diencephalon as well is still an open question. We have not been able to find any such changes.

9. Morgagni's syndrome is on the whole only slightly pathological and, in fact, need not be accompanied by any clinical symptom at all. The symptomatology of frontal hyperostosis, as described by various authors, is scarcely characteristic and seems primarily to be connected with the changes generally observed in the ageing woman The miscellaneous symptomatology described in the literature was present in our cases of frontal hyperostosis as well. The majority of these symptoms can, however, be explained by the often present hypertension and by organic brain changes of various kinds. As the biological connection between the clinical symptoms and the organic changes found at the post-mortem examinations is fairly loose both in Morgagni's syndrome and in frontal hyperostosis, we cannot accept the proposal of a special "Stewart-Morel's syndrome" (hyperostosis frontalis interna with adiposity and cerebral disturbances).

10. As frontal hyperostosis, the principal characteristic of Morgagni's syndrome, may be considered an inconstant sex characteristic on account of its frequent occurrence in women after the menopause, it can also be used for the determination of skull fragments, for example, in paleopathology.

CHAPTER EIGHT

SUMMARY AND CONCLUSIONS

1. An endocrine syndrome has been described which covers the *triad*: *Hyperostosis frontalis interna*, *virilism* and *obesity*. In 1936 we suggested as a suitable term "*Morgagni's syndrome*," as this great scientist gave the first classical description of a typical case.

2. The present investigations are based on a series of 1,000 female skulls, from post-mortem examinations, with a control examination of the same number of male skulls. An objective picture of the syndrome can be obtained only by post-mortem cases; purely clinical cases may easily induce an erroneous conception.

3. Morgagni's syndrome is a symptom complex occurring very often in women after the menopause. It may also be observed, although less frequently, in younger women, and then not infrequently in connection with other endocrine disturbances. There are only a few cases of a corresponding triad in men verified at autopsy; here, too, other endocrine disorders may be present at the same time.

4. In the present post-mortem material the principal characteristic of Morgagni's syndrome, frontal hyperostosis, was observed in about 40 per cent of women after the menopause, at any rate if the slighter degrees are also included Its frequency increases in later age groups, from about 30 per cent between 56 and 60 years to 51 per cent. between 71 and 80 years. Severe cases are not uncommon; a pronounced or very pronounced hyperostosis was observed in about one-third of the cases with this skull change.

5. The second characteristic of the triad, the virilism, comprises, when complete, both hirutism of the face and coarse masculine features, but is mostly limited to hirsutism only. The third characteristic, the obesity, may be very excessive

6. Morgagni's triad belongs to the family of pituitary syndromes. In this connection the analogy with the symptom complex of the pregnant woman, the "pregnancy syndrome," is particularly striking. The triad also presents remarkable analogies with other pituitary symptom complexes, e g., Pierre Marie's syndrome (acromegaly), Cushing's syndrome and Frohlich's syndrome (dystrophia adiposogenitalis); transitions to and combinations with these syndromes and other endocrine disorders are also often observed

7. Frontal hyperostosis is not infrequently combined with a general or frontoparietal thickening of the skull, but fundamentally it should be kept apart from the latter

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